CHEMICAL ANATOMY
PHYSIOLOGY AND PATHOLOGY
OF
EXTRACELLULAR FLUID

A LECTURE SYLLABUS

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"The living organism does not really exist in the milieu extérieur (the atmosphere if it breathes, salt or fresh water if that is its element) but in the liquid milieu intérieur formed by the circulating organic liquid which surrounds and bathes all the tissue elements; this is the lymph or plasma, the liquid part of the blood which, in the higher animals, is diffused through the tissues and forms the ensemble of the intercellular liquids and is the basis of all local nutrition and the common factor of all elementary exchanges.

The stability of the milieu intérieur is the primary condition for freedom and independence of existence; the mechanism which allows of this is that which ensures in the milieu intérieur the maintenance of all the conditions necessary to the life of the elements."

Claude Bernard

"This theory of the constancy of the milieu intérieur was an induction from relatively few facts, but the discoveries of the last fifty years and the introduction of physico-chemical methods into physiology have proved that it is well founded."

Lawrence Henderson

UNITS OF MEASUREMENT

In studying the chemical structure of extracellular fluid, measurements of its components must obviously be stated in terms of chemical equivalence. Only in this way can their relative magnitudes and inter-relationship be correctly displayed. The suitable term is milliequivalents per liter. This value is obtained by dividing milligrams per liter by atomic weight and multiplying by valency.

The form of statement for measurements of the inorganic ions which usage has unfortunately imposed is milligrams per cent. Conversion to milliequivalents per liter for the individual ions is as follows:

$Na^{\cdot}$	mg.	per 100 cc.	x 10	÷ 23
$K^{\cdot}$	"	"	"	÷ 39
$Ca^{\cdot\cdot}$	"	"	"	÷ 40 x 2
$Mg^{\cdot\cdot}$	"	"	"	÷ 24 x 2
Cl'	"	"	"	÷ 35
HPO_4''	(mg. P)	"	"	÷ 31 x 1.8
SO_4''	(mg. S)	"	"	÷ 32 x 2

The valency of HPO_4 is taken as 1.8 because, at the normal pH of extracellular fluid, 20% of the concentration of this radical carries one equivalent of base, (BH_2PO_4), and 80% two equivalents, (B_2HPO_4); B representing univalent base. Base equivalence per unit of (HPO_4) is therefore $0.2 + (0.8 \times 2) = 1.8$. The double valency sign is to this small extent inaccurate.

For the concentrations of carbonic acid ($H.HCO_3$) and of bicarbonate ($B.HCO_3$) convention prescribes the cumbersome statements: volume per cent CO_2 as carbonic acid and volume per cent CO_2 as bicarbonate. These volume per cent values are converted to milliequivalents per liter by dividing by 2.22.

The base equivalence of protein as milliequivalents per liter is obtained by multiplying grams protein per 100 cc. by the Van Slyke factor, 2.43.

UNITS OF MEASUREMENT (Continued)

In studying the osmotic features of extracellular fluid measurements of its components are stated in terms of ionic concentration. In other words valency is disregarded. The suitable term is milliosmols per liter (milligrams per liter divided by atomic weight). The milliosmolar and milliequivalence values for the univalent ions are obviously identical. The chemical equivalence of the divalent ions is twice their milliosmolar value. The term milliosmolar is used instead of millimolar to make clear the additive osmotic effect of individual ions; e.g., the milliosmolar value of of a solution of sodium chloride is twice its millimolar value.

CHARTS

CHART 1

Extracellular fluid is composed of the plasma of the blood and the interstitial fluid (including lymph) which lies between the vascular compartment and the tissue cells. Functionally considered extracellular fluid is a particularly clear cut entity. Its physiological role is as evident as that of the nervous system, for instance, and its organization to this end is quite as ingenious. Extracellular fluid constitutes, as Claude Bernard appreciated, the immediate environment of the organism. It replaces, and in its essential features still closely resembles, the external environment (sea water) of the early forms of life. This aqueous medium which surrounds the tissue cells is the vehicle of transport of nutrient and waste materials. Besides this simple service, it provides stability of physico-chemical conditions, such as reaction in terms of hydrogen ion concentration, osmotic pressure, and temperature. The values for these properties in cell fluid rest on the values at which they are held in the surrounding medium and the successful operation of vital processes requires an approximate constancy.

Establishment of an internal aqueous environment in which physical properties are held nearly stationary in the presence of a widely irregular demand for transport of many and various chemical substances, required, besides an intrinsic suitability of the medium itself, the invention of intricate apparatus of support and control. Movement of the medium throughout the body is accomplished by the cardio-vascular mechanism. A voluminous portal, the lungs, permits gaseous exchange with the external environment. A special vehicle, the red blood cells, containing a substance, hemoglobin, endowed with a reversible affinity for oxygen and carbon dioxide, provides the necessary rapidity of transport of these two components of the largest metabolic transaction in the body, the oxidation of food substances. A remarkable organ of regulation, the kidney sustains the chemical structure of extracellular fluid. MacCallum, regarding the establishment of the enclosed aqueous medium as the largest forward step in the history of the animal organism, has described the kidney as the organ par excellence of evolution.

The total quantity of extracellular fluid is about twenty per cent of body weight. As shown in the chart, one quarter lies in the vascular compartment and three quarters in the interstitial space. The volume of fluid in the tissue cells of the body is roughly fifty percent of body weight; two and one-half times the volume of the surrounding medium. Incoming substances enter the plasma and it is this more rapidly circulating portion which is directly dealt with by the mechanisms of regulation. On the arterial side

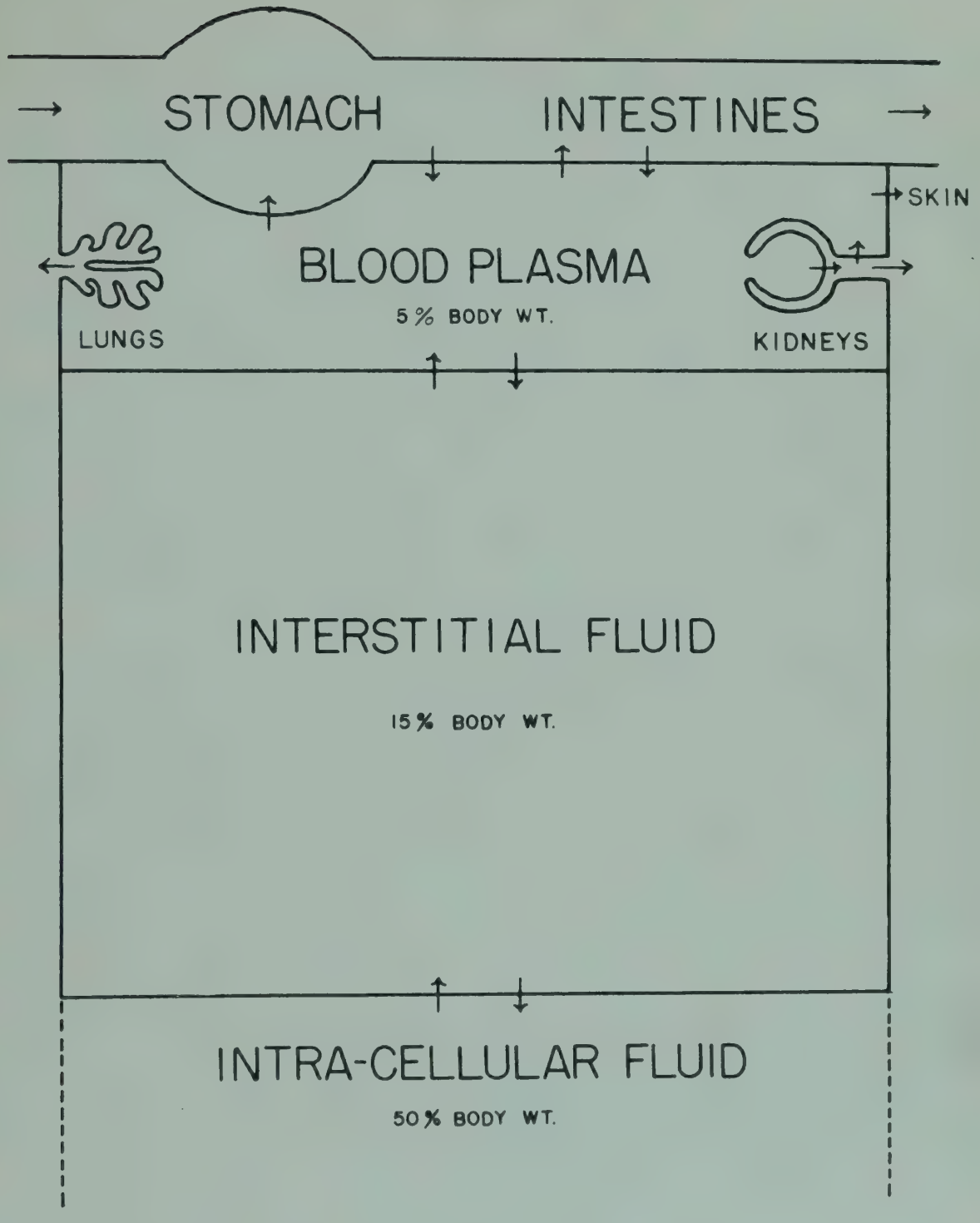

STOMACH
INTESTINES
SKIN
BLOOD PLASMA
5% BODY WT.
LUNGS
KIDNEYS
INTERSTITIAL FLUID
15% BODY WT.
INTRA-CELLULAR FLUID
50% BODY WT.

CHART I

of the capillary bed, fluid moves into the interstitial space under hydrostatic pressure produced by the work of the heart. On the venous side, the osmotic differential provided by the plasma proteins is unopposed and sustains a return flow into the vascular compartment. The chemical continuity of extracellular fluid is shown in the next chart.

CHART 2

These diagrams describe the chemical anatomy of extracellular fluid (blood plasma and interstitial fluid) and also of sea water and of cell fluid, in terms of acid-base equivalence. The individual values for the cations or potential base are superimposed in the left hand columns and those for the anions or acid radicals in the right hand columns. The value for a component may be read on the outer side of the ordinate. The scale on the inner side refers to the total of equivalence (the sum of the values in both columns). The values are per liter of water; in other words the space occupied by protein is discarded.

The two middle diagrams make clear the almost identical chemical patterns of blood plasma and interstitial fluid. The only large item of difference is the relatively very small quantity of the non-diffusible component, protein, in interstitial fluid. This makes necessary adjustment of the concentrations of the diffusible ions which will preserve total cation-anion equivalence (Donnan equilibrium). Replacement in interstitial fluid of the base equivalence of plasma protein is accomplished, as shown in the diagrams, by a balanced reduction of cation and increase in diffusible anion, with the result that the total of equivalents in plasma stands above that in extracellular fluid by approximately the base equivalence of plasma protein (16 milli-equivalents per liter). Owing to its multivalency, the chemical equivalence of protein is about 8 times its concentration value. The difference between the two fluids in the later term is therefore approximately 2 milliosmols per liter. This small difference has a large importance with respect to extracellular fluid circulation (Chart 1). The presence of the device of a non-diffusible plasma component to propel fluid exchange between the two compartments does not, of course, disturb the conception of extracellular fluid as a continuous and essentially uniform medium.

A total value for the non-electrolytes (nutrient substances; glucose, amino-acids, etc., and waste products of protein metabolism) is placed across the top of the diagrams. As compared

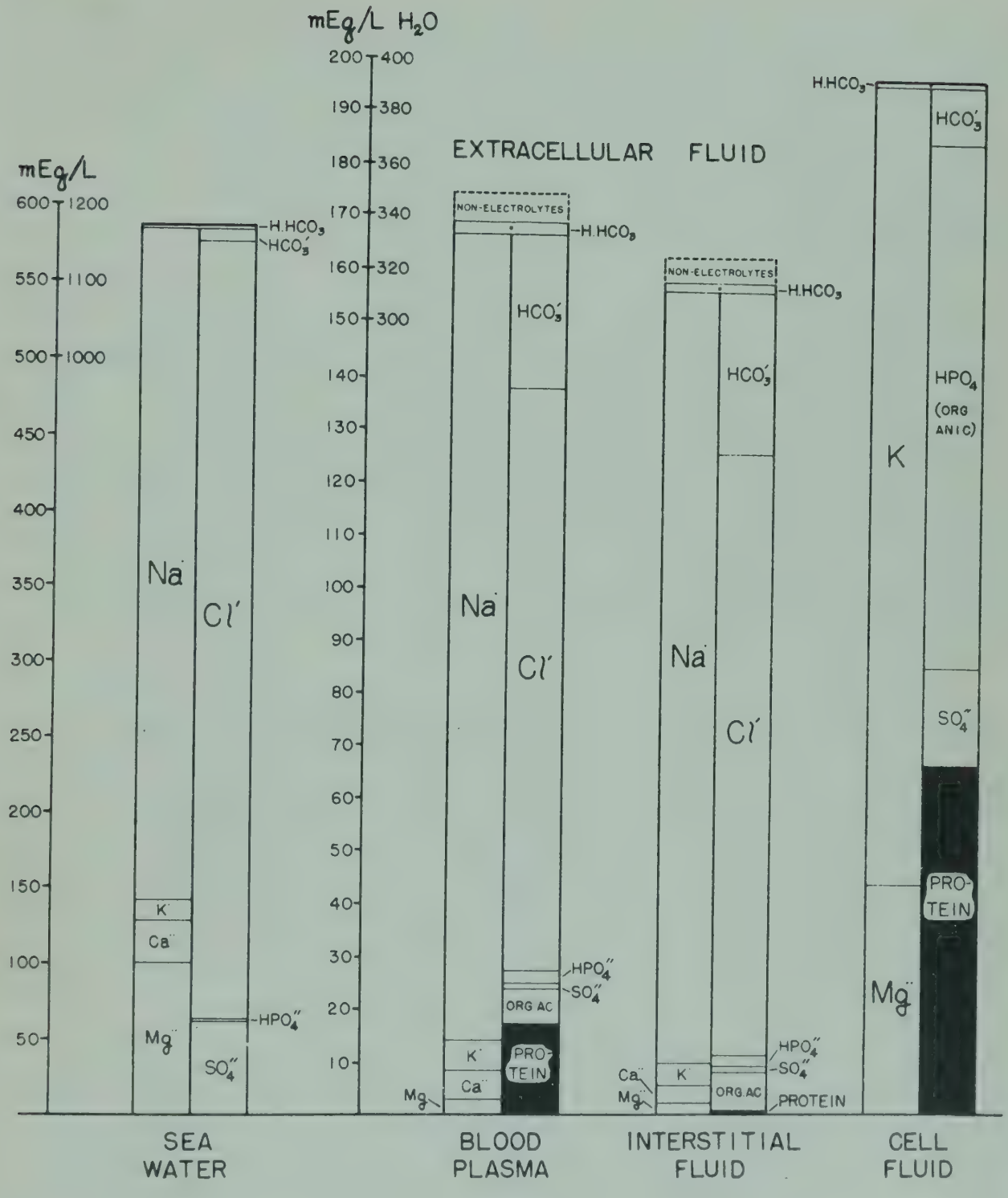

mEq/L H2O
mEq/L
EXTRACELLULAR FLUID
NON-ELECTROLYTES
H.HCO3
HCO3'
Na'
Cl'
K'
Ca''
Mg''
HPO4''
SO4''
ORG AC
PRO-TEIN
ORG.AC
PROTEIN
HPO4 (ORGANIC)
K
SEA WATER
BLOOD PLASMA
INTERSTITIAL FLUID
CELL FLUID

CHART 2

with the electrolytes, these substances occupy a relatively very small amount of space, in terms of concentration, although the total quantity of them carried to the tissue cells and into the urine over a unit of time is several times larger. The non-electrolytes demand only expeditious conveyance. The electrolytes constitute a chemical framework on which rests the stability of the physical properties of extracellular fluid. Their transport is in terms of this requirement. This is the meaning of the large prominence of the electrolytes.

The history of extracellular fluid is clearly indicated by the resemblance of its chemical pattern to that of sea water. In the sea water diagram may be seen the same four components of total base, the same dominance by sodium and chloride ion, and same pair of buffering substances, carbonic acid and bicarbonate. The chemical skeleton of sea water is clearly visible in extracellular fluid. The total ionic concentration of sea water is several times that of extracellular fluid. Since the salinity of the sea is known to have increased continuously, the surmise is permissible that the electrolyte concentration found in extracellular fluid corresponds with that of sea water at the time of establishment of internal aqueous environment.

That extracellular fluid is a surrounding and not a pervading medium is evident from the widely different electrolyte composition of cell fluid. The data used in constructing this diagram are to some extent conjectural but will serve to present the extraordinary phenomenon of apparently complete independence as regards ionic pattern in the two intimately adjacent and osmotically balanced fluids. An important feature is that the two largest components of extracellular fluid, sodium and chloride ion, are not permitted to pass the boundaries of protoplasm. With some slight reservation as regards sodium, an exclusively extracellular position of these two ions has been dependably established.

The foregoing description of the chemical structure of extracellular fluid is in terms of average values found in health. The basis of stability of physical properties is the degree of constancy of chemical pattern which can be maintained. With a quite perfect constancy, hydrogen ion concentration and osmotic pressure would be immovable. Since, however, water and substances enter extracellular fluid intermittently and in widely irregular quantities and since renal adjustments require an appreciable interval of time, concentration values for the individual components of extra-

cellular fluid cannot be maintained with an ideal precision. Even under the most favorable circumstances, small oscillations will be unavoidable and, in the presence of obstacles imposed by disease, large deviations may develop. Inaccuracies in the control of composition are not, however, permitted to exert their full effect on physical properties. The regulatory apparatus governing extracellular fluid possesses mechanisms of adjustment behind the kidney which do not prevent but which greatly limit change in physical properties in the presence of change in chemical pattern. From the description of the operation of these mechanisms which follows (Charts 4-14) it will be noted that the extent to which their defense of physical properties falls short is roughly proportional to the initial error in control of chemical structure. Rigidity, then, is not to be expected either in chemical structure or in physical properties. The cardinal merit of any physico-chemical system in the body must be resiliency; otherwise it would be sure to be smashed by the rapidly changing currents of chemical events. In order to survive severely adverse circumstances, this recoverability from distortion must have a width far beyond the usual requirement. The physico-chemical system in extracellular fluid exhibits this necessary elasticity very beautifully.

Degree of success of the regulatory mechanisms which guard the chemical structure of extracellular fluid may be judged by the measurements of the components of its accessible portion, the blood plasma. Except for carbonic acid, which is controlled by the respiratory mechanism,and plasma protein, which is governed by a mechanism not yet visible,all of the items of plasma structure shown in the diagram are under renal control. The normal values are given as milliequivalents per liter of plasma instead of per liter of water as in the preceding chart. Plasma water is obviously the correct basis for a statement of concentration. Its precise definition, however, requires that measurement of a plasma substance be accompanied by determination of plasma specific gravity, or, as an approximation, the concentration of protein. Usage has therefore understandably chosen the much more convenient reference to plasma volume. This form of statement is satisfactory for most purposes of plasma study.

The diagram is constructed by superimposing the individual values for the cations in the left-hand column and those for the anions in the right-hand column. The diagram provides a view of the various parts of the acid-base structure in true perspective as regards their relative magnitudes. It may be noted that nearly all of the base (91%) is sodium and that chloride is the largest component of the total acid value. The next largest item of structure is the concentration of bicarbonate ion (HCO_3') which together with the base which it covers constitutes the plasma bicarbonate. The value for the sum of organic anions in the plasma is taken as the difference between the sum of the other ions and total base. A practicable method for its direct determination is not at hand,although several components may be readily measured. The line down the center of the diagram correctly indicates that we have to deal in the plasma, not with salts, but with separately controlled quantities of individual ions. The slight, instead of practically complete, dissociation of carbonic acid is the single exception to this statement. This is crudely indicated by placing a dot instead or a line between its component ions. The plasma values given in the chart have been established as average in health. They are not rigidly sustained; oscillations, however, under normal circumstances are relatively very small.

ACID-BASE COMPOSITION OF BLOOD PLASMA

BASE	mEq/L
$Na^{\cdot}$	142
$K^{\cdot}$	5
$Ca^{\cdot\cdot}$	5
$Mg^{\cdot\cdot}$	3
	155

ACID	mEq/L
$HCO_3^{\prime}$	27
$Cl^{\prime}$	103
$HPO_4^{\prime\prime}$	2
$SO_4^{\prime\prime}$	1
ORG. AC	6
PROTEIN	16
	155

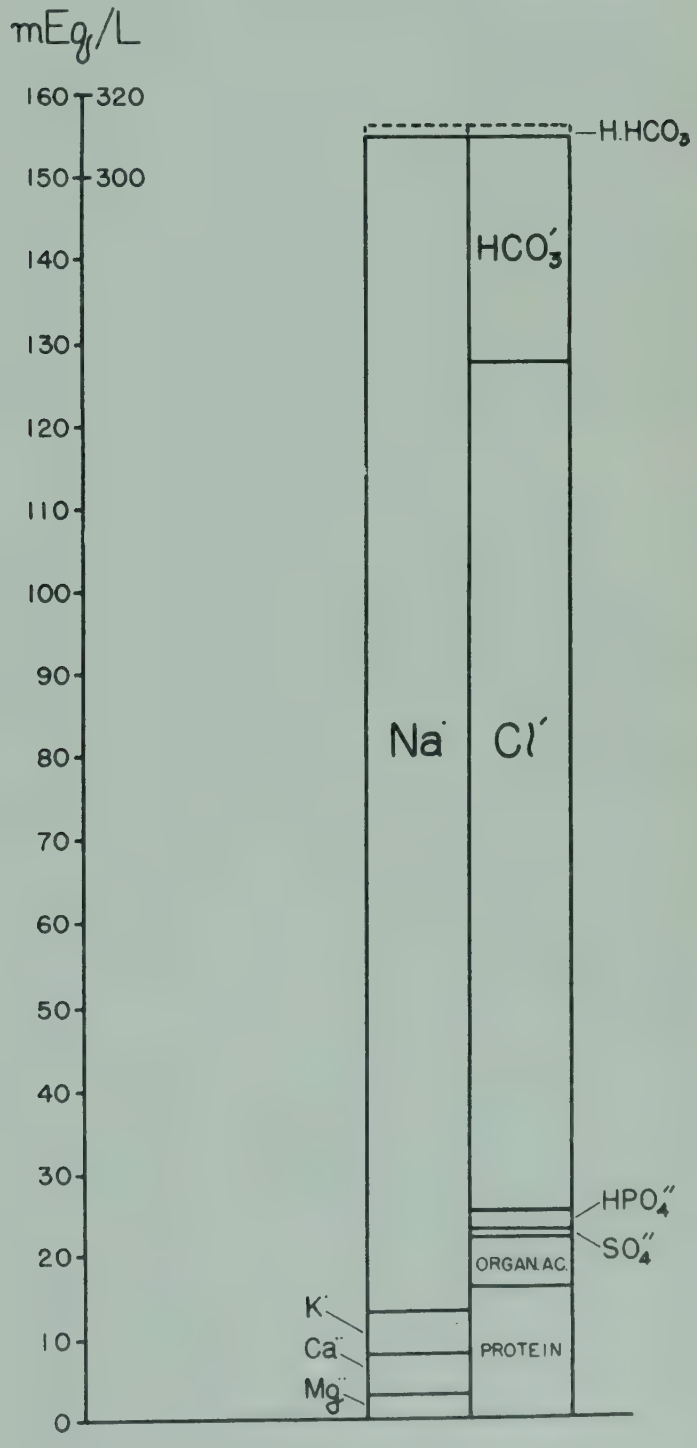


CHART 3

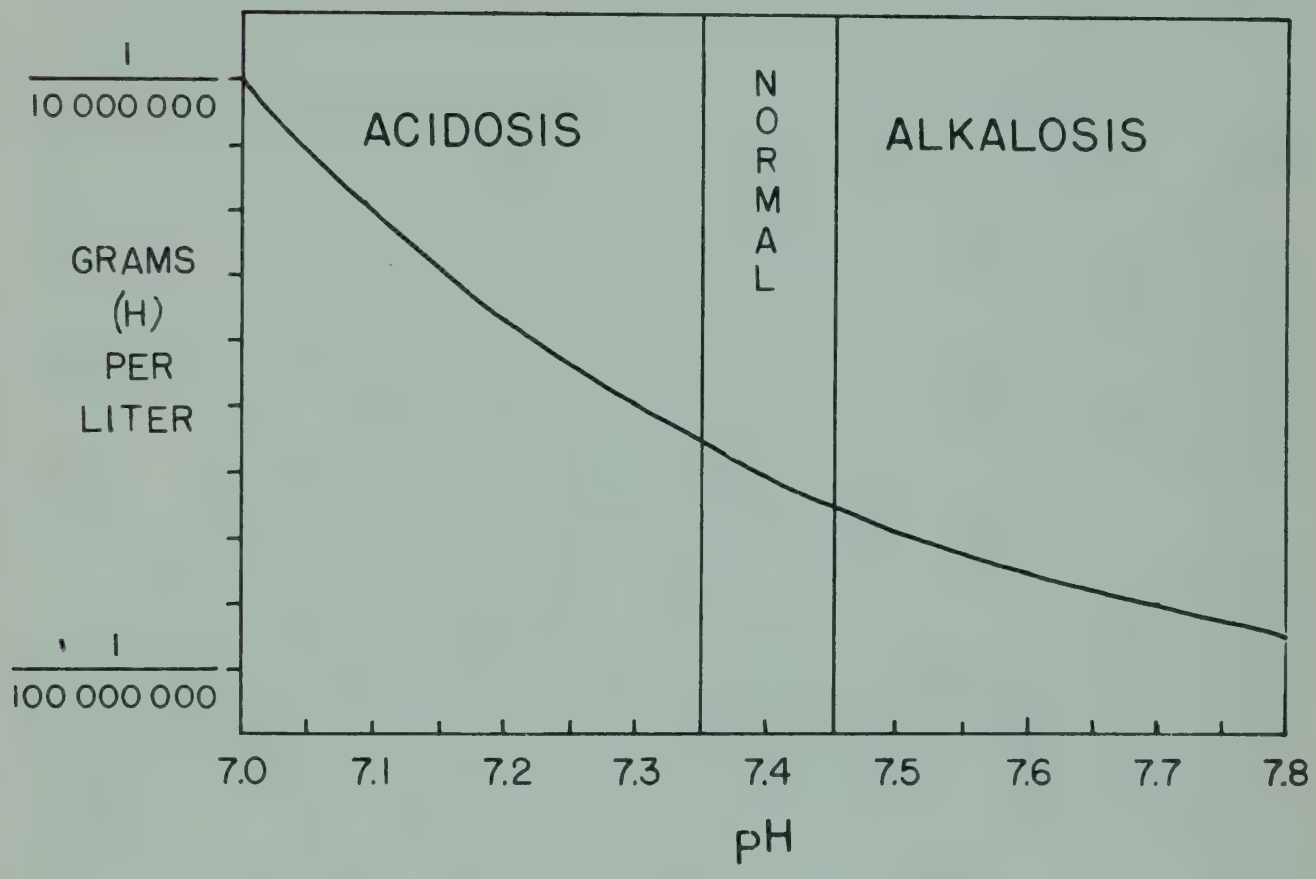
CHART 3 (Continued)

Since about nine-tenths of the chemical skeleton of the plasma is built of univalent ions, the diagram provides an approximate description in terms of ionic concentration as well as of chemical equivalence. Total ionic concentration, derived from the data in the chart after dividing the values for the divalent ions by 2 and the value for protein by 8, is 290.5 milliosmols per liter. In studying osmotic mechanisms of the body fluids, ionic concentration is more suitably stated per liter of water. Assuming a plasma protein content of 6.5 per cent, plasma water is 93.5 per cent of plasma volume and total ionic concentration per liter of plasma water is 290.5 x 100/93.5 = 311 m-osM./L. Subtracting 2 m-osM. per liter for protein (chart 2), ionic concentration of interstitial fluid is 309 m-OsM./L. For extracellular fluid as a whole, 310 m-osM./L. may therefore be taken as the normal value for ionic concentration.

CHART 4

The range of hydrogen ion concentration compatible with life is approximately from one ten millionth to one hundred millionth of a gram per liter. Although these are extremely minute quantities, they define a generous (almost ten fold) width of permissible change. Using the pH notation system the extreme limits of reaction are pH 7.0 and pH 7.8. The entire physiological range of reaction thus lies on the alkaline side of neutrality, pH 7.0. In health hydrogen ion concentration is held within narrow limits which have been somewhat arbitrarily defined as pH 7.35 and pH 7.45. There is thus left on either side wide regions of change designated Acidosis and Alkalosis from which hydrogen ion concentration can return to its optimal position if the circumstances which caused its departure are removable.

The basis of control of ionized hydrogen at the ultraminute concentration which biological processes require is the almost uniquely small extent of hydrogen dissociation from the largest end product of metabolism, carbonic acid. This extremely weakly acid substance pervades the body fluids at a level controlled by the respiratory mechanism. In the presence of its salt, the slight extent of dissociation of hydrogen from carbonic acid becomes still smaller. This is due to "common ion effect" which consists in disturbance of the dissociation equilibrium of carbonic acid by addition of (HCO'_3) from bicarbonate. This makes necessary a new position of balance in which the concentration of molecular carbonic acid, ($H.HCO_3$), is increased at the expense of (H) and (HCO'_3). By this process hydrogen ion concentration is reduced.



COMMON ION EFFECT:

$$(H.HCO_3) \rightleftharpoons (\overset{+}{H})(H\overset{-}{C}O_3)$$

$$(B.HCO_3) \rightleftharpoons (\overset{+}{B})(H\overset{-}{C}O_3)$$

CHART 4

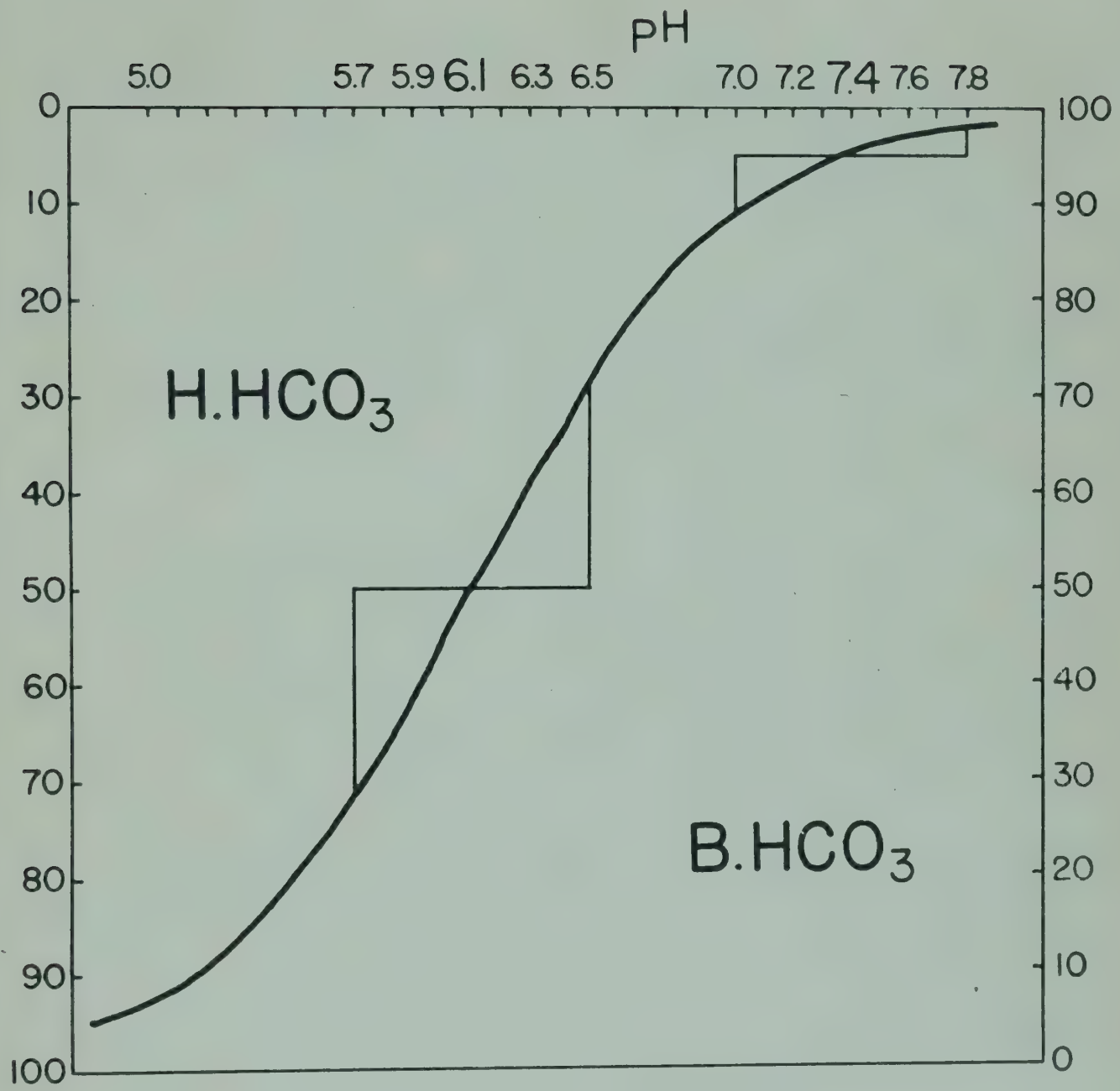
Common ion effect explains the "alkaline salt" character of bicarbonate and makes clear the relationship between hydrogen ion concentration and the ratio of the concentrations of carbonic acid and bicarbonate in a solution containing these substances. This relationship is not linear. It is described by the S shaped curve in the chart. The shape of the curve has an important implication with respect to the buffering capacity of a carbonic acid-bicarbonate solution. The transaction known as "buffering" consists in the substitution of a weakly acid substance (from which $\dot{H}$ dissociates to a very slight extent) for a strongly acid substance (from which $\dot{H}$ dissociates more or less completely) entering the solution, or in the case of strong base, the substitution of a weakly alkaline substance. To illustrate the process of these substitutions in a solution containing carbonic acid and bicarbonate:

1. $HCl + NaHCO_3 = NaCl + H_2CO_3$
2. $NaOH + H_2CO_3 = H_2O + NaHCO_3$

(It will be understood that these equations are simplified statements. The substances are not present as such in solution. They interact with each other and with water by way of a system of dissociation equilibria which determines the concentrations of hydroxyl ion ($\bar{O}H$) and hydrogen ion ($\dot{H}$). These have a reciprocal relationship.)

In (1), H.Cl, from which ($\dot{H}$) practically completely dissociates, is replaced by $H.HCO_3$ which releases ($\dot{H}$) to a relatively minute extent. In (2), large reciprocal reduction of ($\dot{H}$) by ($\bar{O}H$) from Na.OH is avoided by substituting the greatly less depressant common ion effect of $Na.HCO_3$. In these buffering processes, $H.HCO_3$ is obtained at the expense of $Na.HCO_3$ (equation 1) and vice versa (equation 2).

The buffering capacity of a carbonic acid-bicarbonate solution, i.e., its effectiveness in limiting movement of pH when acid or alkali enters the solution, is measured by the extent of the reciprocal change in ($H.HCO_3$) and ($B.HCO_3$) for a given change in pH. Owing to the shape of the pH-ratio curve, buffering capacity depends on the initial position of pH. This is illustrated in the chart. The physiological range of pH is at the top of the curve where it has begun to flatten out, i.e., steps in reciprocal change in ($H.HCO_3$) and ($B.HCO_3$) become progressively smaller with respect to



$$pH = 6.1 + LOG. \frac{B.HCO_3}{H.HCO_3}$$

(HENDERSON - HASSELBALCH EQUATION)

CHART 5-a

pH change. In other words, there is decline in the quantities of added acid or alkali required to produce a unit of pH change. To produce the same width of pH change over the steep part of the curve, much larger additions of acid or alkali are required. As shown by the vertical lines in the chart, the buffering capacity of a carbonic acid-bicarbonate solution of pH 6.1 is about four times that of a solution of pH 7.4.

Apparently carbonic acid-bicarbonate buffering in biological fluids is relatively inefficient and the normal position of pH unfortunate. Actually, as will be shown, owing to respiratory control of ($H.HCO_3$), buffering is remarkably effective and pH 7.4 has a particular security.

CHART 5-b

Owing to an inverse proportionality of hydrogen ion dissociation to change in concentration of $H.HCO_3$, the pH-ratio relationship shown in the preceding chart is independent of the absolute values for ($H.HCO_3$) and ($B.HCO_3$). This circumstance is of large convenience to reaction regulation. It means that, in order to provide pH 7.4, it is not necessary to sustain fixed values for ($H.HCO_3$) and ($B.HCO_3$); preservation of the ratio is all that is required. This permits defense of the normal hydrogen ion concentration in the presence of irreversible, or temporarily irreversible, change in one component of the ratio by adjustment of the other component in the direction which will restore the normal ratio. The physiological advantage of this method of regulation is evident; unimpaired mechanisms of control are permitted to compensate for those which are disabled.

At pH 7.4, the curve (chart 5-a) defines for ($H.HCO_3$) and ($B.HCO_3$) a 1:20 ratio. In extracellular fluid this ratio is, under normal circumstances, provided by 1.35 m-eq./L. ($H.HCO_3$) and 27 m-eq./L. ($B.HCO_3$). These values are more usually stated as 3 vol. % and 60 vol. % CO_2; but less suitably since, in this term, quantitive relationship with other components of the ionic structure of the plasma is not displayed. The concentration of carbonic acid is governed by the respiratory mechanism. Reaction change resulting

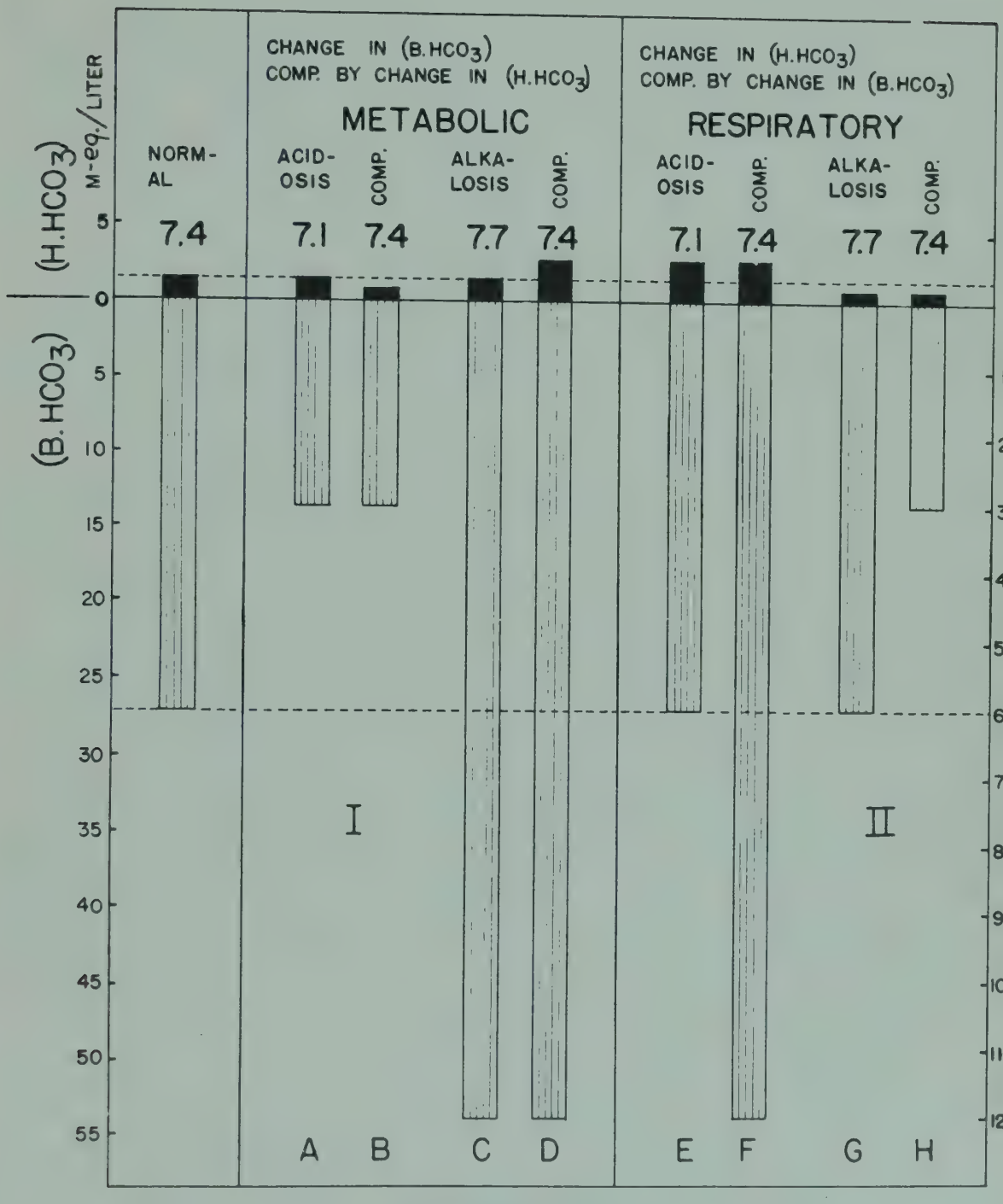

(H.HCO3) M-eq./LITER
(B.HCO3)
VOL. % CO2
NORM-AL
7.4
CHANGE IN (B.HCO3) COMP. BY CHANGE IN (H.HCO3)
METABOLIC
ACID-OSIS
7.1
COMP.
7.4
ALKA-LOSIS
7.7
COMP.
7.4
CHANGE IN (H.HCO3) COMP. BY CHANGE IN (B.HCO3)
RESPIRATORY
ACID-OSIS
7.1
COMP.
7.4
ALKA-LOSIS
7.7
COMP.
7.4
I
II
A
B
C
D
E
F
G
H

CHART 5-b

from an incorrect ($H.HCO_3$) is therefore appropriately described as "respiratory" acidosis or alkalosis. Compensation consists in corresponding change in ($B.HCO_3$). Disturbance of respiratory control of ($H.HCO_3$) is relatively infrequent. The usual cause of ratio alteration is change in its other component, ($B.HCO_3$). Change in ($B.HCO_3$),as will be shown in the next chart, is secondary to change in other parts of the ionic structure of the plasma. The resulting acidosis or alkalosis is described as "metabolic". This is a not quite suitable term, since the underlying change in plasma structure may result not only from abnormal metabolic events (e.g. ketosis) but also from impairment of regulatory mechanisms (e.g. renal disease). Defense of the ratio is provided by alteration of ($H.HCO_3$).

The diagrams in the chart explain reaction disturbance from ratio change and defense of reaction by ratio restoration. In Section I, the cause of reaction change is departure of ($B.HCO_3$) from its usual value. Compensation for reduction of ($B.HCO_3$) by one-half is obtained by lowering ($H.HCO_3$) to one-half of its normal value, a⟶b; and for a two-fold increase of ($B.HCO_3$) by doubling ($H.HCO_3$),c⟶d. In Section II, control of ($H.HCO_3$) is at fault and is shown in the diagrams as fixed at double and at one-half of its normal value. Compensation is provided by corresponding change in ($B.HCO_3$). For the sake of simplified illustration, the diagrams describe complete compensation. Actually, ratio defense almost always falls considerably short of the mark. So that, in the presence of large change in ($B.HCO_3$), or in ($H.HCO_3$), departure of pH from 7.4 is not prevented although it is greatly limited.

The simplest and most dependable measurement for demonstration of acidosis or alkalosis is the total CO_2 content of the plasma, i.e., the CO_2 released from $H.HCO_3$ and $B.HCO_3$ by adding strong acid to the plasma in the Van Slyke burette. As may be seen in the diagrams, CO_2 from $H.HCO_3$ will be a small fraction of total CO_2. Change in total CO_2 from its usual value (63 vol.%) therefore approximately measures change in ($B.HCO_3$). Clinically, acidosis or

alkalosis is nearly always the result of change in bicarbonate (Section I) so that usually a low total CO_2 value dependably indicates acidosis and a high value alkalosis. It must be remembered, however, that when reaction disturbance results from inaccurate respiratory control of ($H.HCO_3$) the changes in total CO_2 have the reverse significance; reduction is compensatory for an underlying alkalosis and extension for acidosis (Section II). The diagnosis of acidosis from a reduced, and of alkalosis from an increased, total CO_2 is therefore not valid unless the circumstances of disease which may cause the usual (metabolic) type of reaction disturbance are demonstrable. In the absence of such evidence the possibility of respiratory acidosis or alkalosis must be considered. A measurement of plasma pH is directly informative. Since ratio repair is almost always incomplete, in the presence of an increased total CO_2, the value for pH will be found on the alkaline side of 7.4 in metabolic alkalosis, and on the acid side in respiratory acidosis. In the case of a reduced total CO_2, a pH below 7.4 indicates metabolic acidosis and above 7.4 respiratory alkalosis. The pH and total CO_2 measurements together thus provide description of the direction of reaction change and degree of compensation. Both measurements are therefore required for an accurate analysis of reaction disturbance.

Stability of hydrogen ion concentration in extracellular fluid thus does not require maintenance of fixed values for ($H.HCO_3$) and ($B.HCO_3$). Reaction regulation, by being permitted to rest on the ($H.HCO_3$):($B.HCO_3$) ratio, is given a wide flexibility, and its study has the simplicity of explaining the cause for change in one component and the mechanism of compensatory adjustment of the other.

Since pH defines the ratio of the concentrations of $H.HCO_3$ and $B.HCO_3$ in blood plasma, their individual values can be derived from a determination of pH together with the overall measurement of their common ion, $-HCO_3$, which is provided by the so-called "total CO_2", or "CO_2 content", measurement.

This chart presents, on an enlarged scale, the portion of the pH-ratio curve, shown in Chart 5-a, which covers the range of pH in blood plasma. It records ($H.HCO_3$) and ($B.HCO_3$) as per cent of total ($-HCO_3$) and so permits derivation of their absolute values at a given pH from measurement of total CO_2. Examples:

			Total CO_2 30 vol. %
1)	pH 7.05	$H.HCO_3$,	30 x 0.10 = 3 vol. %
		$B.HCO_3$,	30 x 0.90 = 27 vol. %

Metabolic Acidosis. Uncompensated (no reduction of $H.HCO_3$)

2)	pH 7.25	$H.HCO_3$,	30 x 0.066 = 1.98 vol. %
		$B.HCO_3$,	30 x 0.934 = 28.02 vol. %

Metabolic Acidosis. Partial compensation by reduction of $H.HCO_3$.

3)	pH 7.5	$H.HCO_3$,	30 x 0.039 = 1.17 vol. %
		$B.HCO_3$,	30 x 0.961 = 28.83 vol. %

Respiratory Alkalosis. Partial compensation by reduction of $B.HCO_3$.

Definite description of the character, extent, and degree of compensation of reaction disturbances can thus be gained from the two measurements, pH and total CO_2. pH indicates the direction of reaction change, i.e. Acidosis or Alkalosis, but does not measure initial alteration of the $H.HCO_3$:$BHCO_3$ ratio or compensatory adjustment of the unaffected component. This information is provided by the values found for plasma carbonic acid and bicarbonate. Dividing these values expressed as volume per cent CO_2 by 2.22 produces the much more suitable form of statement, milliequivalents per liter.

PARTITION OF TOTAL PLASMA -HCO_3 ("TOTAL CO_2") IN RELATION TO pH

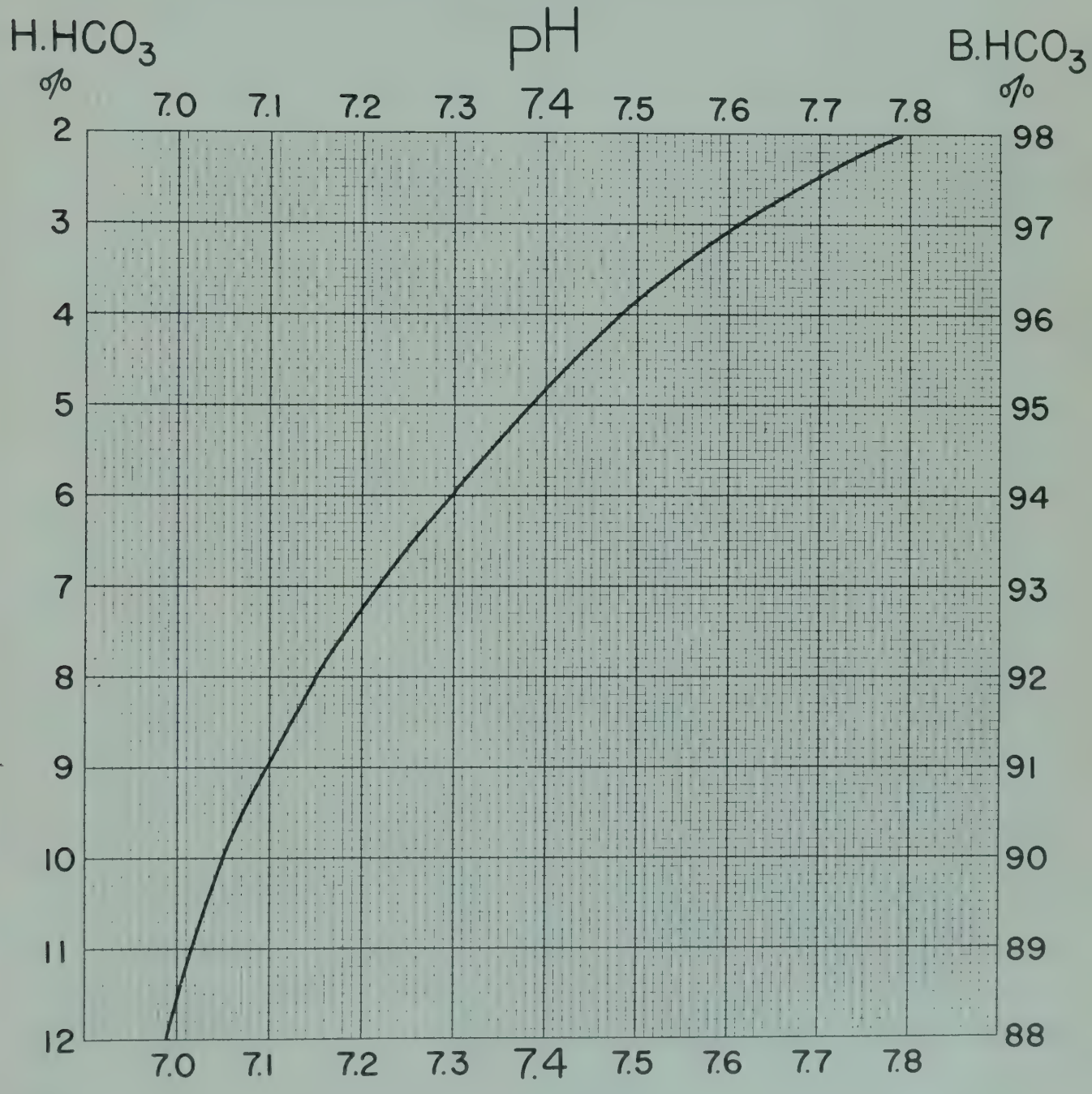


CHART 5-C

The relationship of carbonic acid and bicarbonate to other parts of the acid-base structure of the plasma is shown in this chart. Carbonic acid, governed by the respiratory mechanism, is placed at the top of the diagram. Bicarbonate, owing to adjustability of its anion component, (HCO_3'), to availability of base, rests on integrity of the remainder of the diagram. Change in any part, or parts, of the acid-base structure which it describes will, by altering base availability, cause corresponding change in bicarbonate. Except for protein, all of the components of this structure are under renal control. The normal value for bicarbonate thus rests indirectly on renal regulation. Abnormal circumstances, however, may cause changes in this structure which are beyond correction by the kidney. The process of adjustment of bicarbonate is illustrated in the diagrams. With increase in the sum of the other anions (A) above the normal value (Diagram 2), (HCO_3') is to an equivalent extent dispossesed of base. This bicarbonate ion is released as carbonic acid and falls under the government of the respiratory mechanism. With decrease of (A) there is corresponding increase of (HCO_3') (Diagram 3), the additional bicarbonate ion being derived from ($H.HCO_3$) sustained in the plasma by the respiratory mechanism. A reduction of plasma base (Diagram 4) is at the expense of ($B.HCO_3$). Plasma bicarbonate is thus determined by the extent to which total base (B) stands above the sum of the other anions (A).

These changes in bicarbonate are the result of the process of carbonic acid-bicarbonate buffering described in chart 5-a, which is the first line of defense of plasma reaction against alteration of the normal acid-base structure of the plasma. By providing base for the covering of an increase of acid radicals (Diagram 2) and by preventing an uncovering of base (Diagram 3), reaction change of disastrous degree is avoided. The second line of defense is provided by respiratory adjustment of carbonic acid. In vitro, change in ($B.HCO_3$) causes reciprocal change in ($H.HCO_3$), (Chart 5-a). In plasma ($H.HCO_3$) released by reduction of ($B.HCO_3$) is removed and ($H.HCO_3$) used in extending bicarbonate is replaced. The resulting changes in the ratio are thus greatly less than in vitro. But the respiratory mechanism carries defense of pH further than this. It undertakes to alter ($H.HCO_3$) from its usual value in the direction of restoring the normal ratio. This is roughly indicated in the

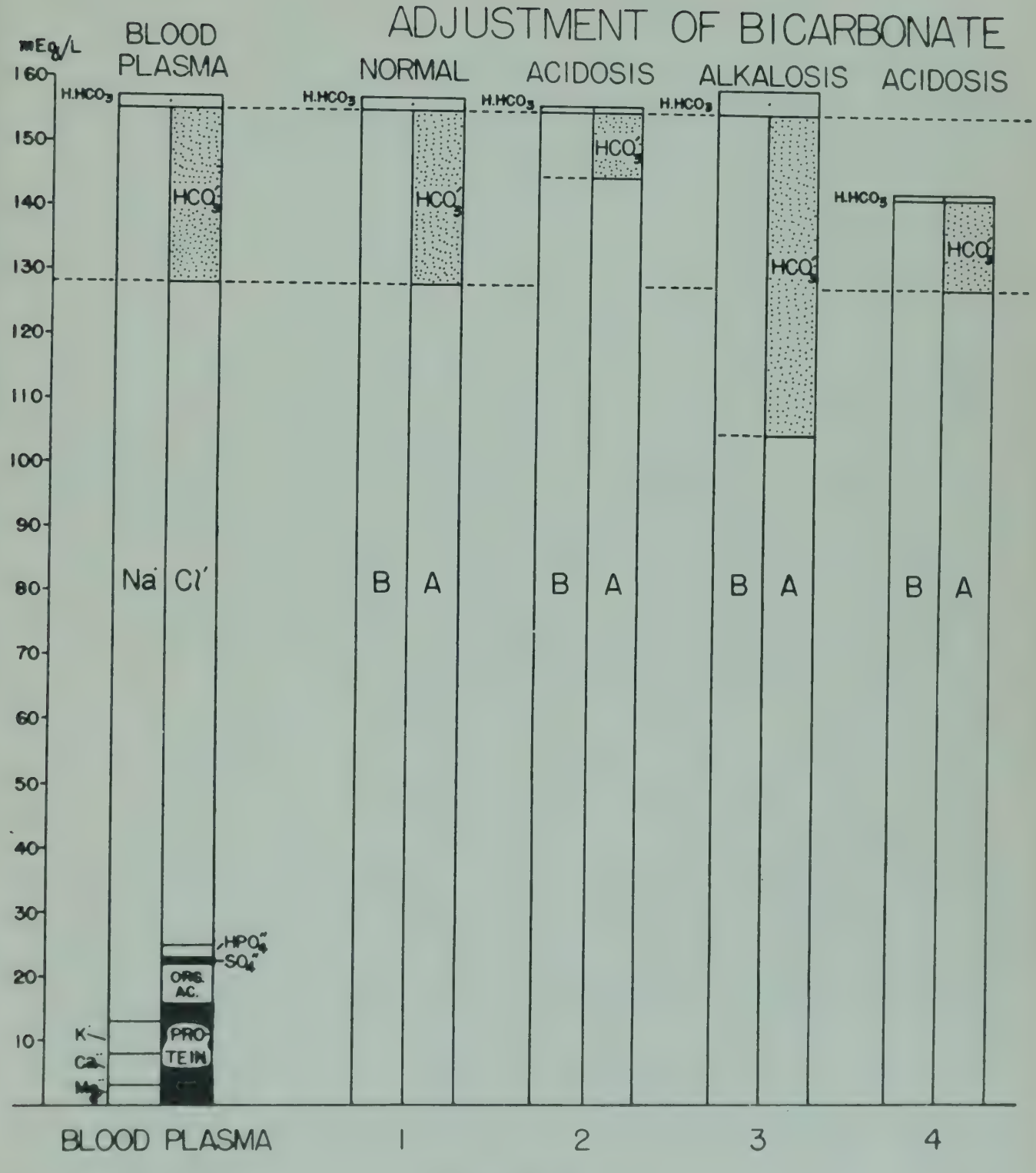

ADJUSTMENT OF BICARBONATE
BLOOD PLASMA
NORMAL
ACIDOSIS
ALKALOSIS
ACIDOSIS
mEq/L
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
H.HCO3
HCO3'
Na'
Cl'
B
A
HPO4"
SO4"
ORG. AC.
PRO TEIN
K'
Ca"
Mg"
BLOOD PLASMA
1
2
3
4

CHART 6

diagrams (see also chart 5-b, section I). Although this adjustment is usually incomplete, it produces a further large limitation of change in pH in the presence of change in ($B.HCO_3$). It will be clear from these diagrams that the change in bicarbonate which is the immediate cause of metabolic acidosis or alkalosis is itself an adjustment made necessary by underlying changes in the acid-base structure of plasma. Carbonic acid-bicarbonate buffering provides the basis of reaction defense. The effect of the incidental change in ($B.HCO_3$) is then minimized by respiratory control of ($H.HCO_3$).

An ideally accurate control of the many individual parts of the ionic structure of the plasma which would hold the B minus A value in the diagram precisely stationary cannot be expected. The adjustability of ($H.CO_3'$) is, therefore, continuously exercised in health as well as disease. It may also be noted that by removal from, or addition to, plasma of $H.CO_3'$ by the respiratory mechanism, gain or loss of anion (A, diagrams 2 and 3) is prevented from causing change in total ionic concentration on which the osmotic value of extracellular fluid almost entirely depends. Respiratory control of carbonic acid thus not only greatly amplifies plasma buffering but also defends the osmotic value and thus exhibits a remarkably comprehensive functional ingenuity.

CHART 7

Because of the control of carbonic acid by the respiratory mechanism, carbonic acid-bicarbonate buffering in blood plasma is enormously more effective than in vitro. This is illustrated by the diagrams in the chart. A reduction of bicarbonate by one-half of its usual value releases 30 vol. % carbonic acid. In vitro, the resulting change in ratio would produce a pH of 6.0, which is far beyond the physiological boundary. With removal of this carbonic acid by way of the lungs, the change in pH is greatly limited and moves only as far as 7.1. The respiratory mechanism then undertakes to further limit movement of pH by changing ($H.HCO_3$) in the direction which will restore the 1:20 ratio, as shown by the remaining diagrams. In the final one, ($H.HCO_3$) is reduced to one-half of its usual value. This produces the usual ratio and pH is completely defended.

STEPS IN $(H.HCO_3)$-$(B.HCO_3)$ BUFFERING IN PLASMA

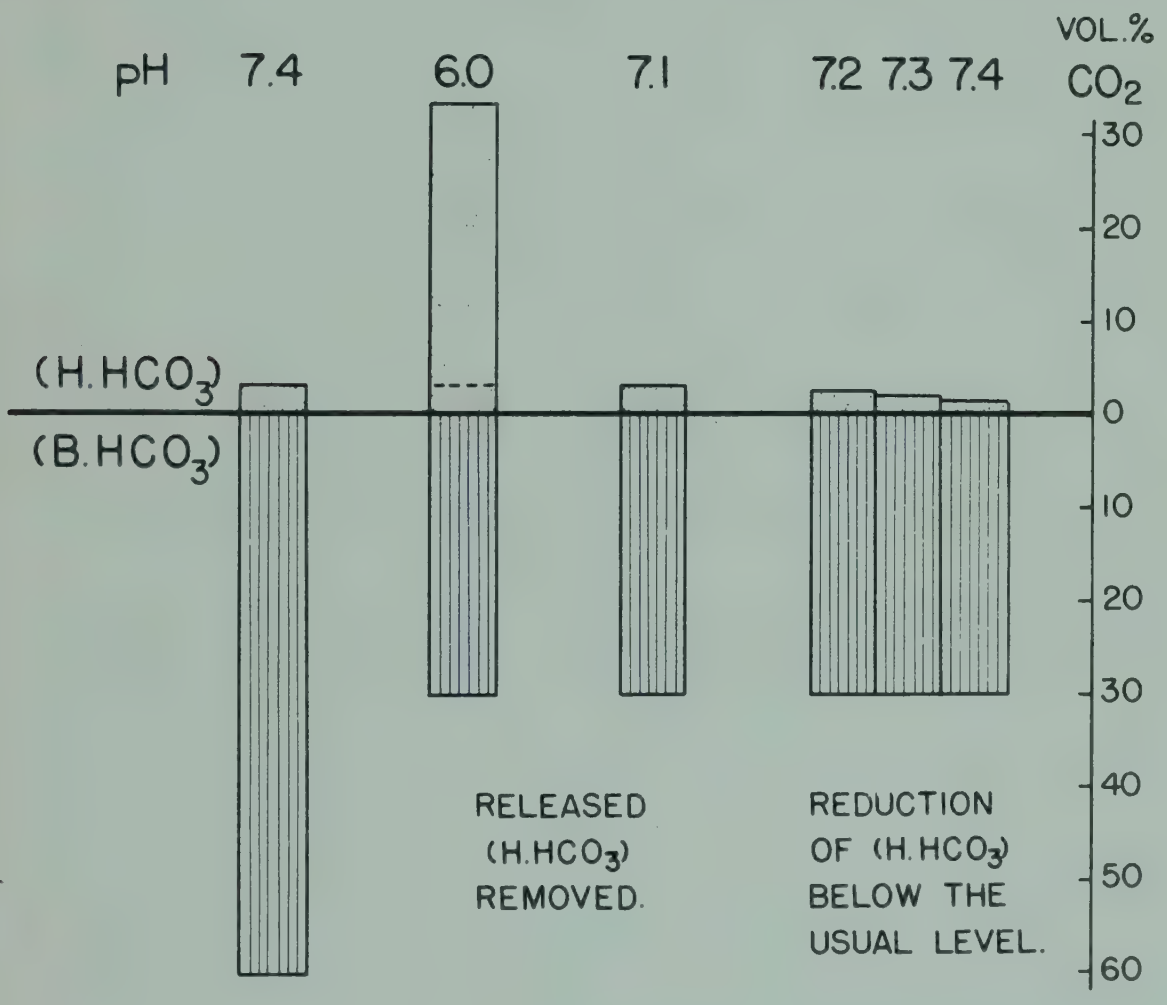


CHART 7

CHART 7 (Continued)

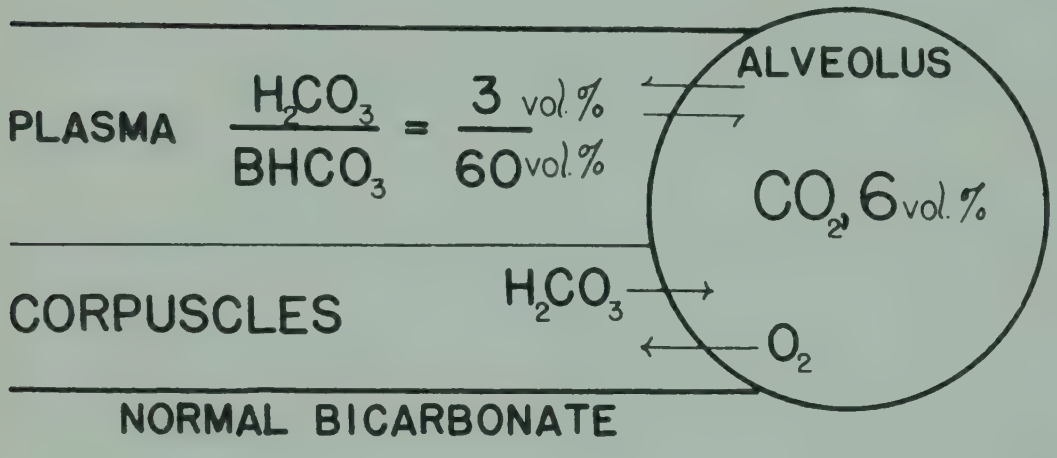
The basis of this adjustment is the direct relationsnip between the concentration of carbonic acid in the plasma and the carbon dioxide tension of the residual air of the lungs to which the plasma is exposed as it flows through the capillary bed of the lungs. The first and very large step in the respiratory defense of pH, the removal of excess carbonic acid requires no effort by the respiratory mechanism. This carbonic acid simply "flows" into the residual air space until plasma concentration comes into balance with the usual CO_2 tension in the residual air. The lungs and the mechanics of their ventilation were designed to sustain this level of CO_2. The second step in defense of plasma pH which involves reduction of alveolar CO_2 tension requires an extensive and laborious alteration of breathing, the method of which is shown in the next chart.

CHART 8

The diagrams describe the mechanism of respiratory adjustment of CO_2 concentration in residual air in the presence of reduction of bicarbonate concentration in blood plasma. In the upper diagram the concentration of $H.HCO_3$ and of $B.HCO_3$ in plasma and of CO_2 in residual air have their usual values. The value for $H.HCO_3$ is one-half that of CO_2 because of the circumstance that the absorption coefficient of CO_2 is 0.52. The diagram implies what is approximately the case viz: that the transport and delivery of carbonic acid to the lungs is accomplished by the red blood cells and that carbonic acid in the plasma is not en route for excretion but is there simply as a physical consequence of exposure of the plasma to the CO_2 tension of the residual air. This is, under normal circumstances, held closely stationary by adjustment of the rate and volume of lung ventilation to the rate of delivery of CO_2 as prescribed by the energy metabolism.

RESPIRATORY REGULATION OF pH OF PLASMA

$$\frac{H_2CO_3}{BHCO_3} = \frac{1}{20} = pH\ 7.4$$



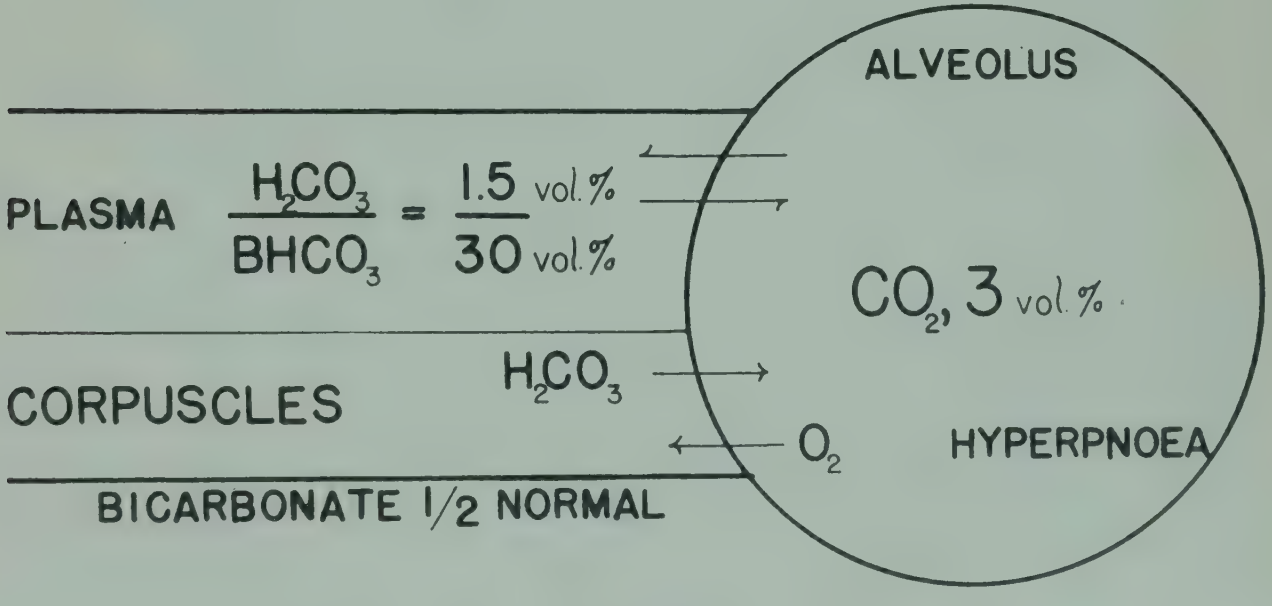


CHART 8

The respiratory adjustment to a reduction of ($B.HCO_3$) to one-half of its usual value, as shown by the lower diagram, consists in doubling the capacity of the residual air space. This reduces CO_2 concentration by one-half and, in consequence, the concentration of $H.HCO_3$ in the plasma falls correspondingly with the result that the normal ($H.HCO_3$):($B.HCO_3$) ratio is preserved and pH is held at 7.4. The large increase in the depth of breathing which sustains the increased volume of residual air is described as hyperpnoea and is the one and only physical sign of acidosis. The concentration of CO_2 may also be reduced by increasing the rate of lung ventilation and in the presence of acidosis there is usually some increase in rate. The dominating and characteristic feature of the change in breathing is, however, the large increase in volume.

When the plasma bicarbonate is above its normal value, respiratory adjustment is in the reverse direction. The breathing of alkalosis is characteristically extremely shallow. The capacity of the residual air space being thus greatly diminished, CO_2 tension and, in consequence, the concentration of $H.HCO_3$ in the plasma rise with the result that the ($H.HCO_3$):($B.HCO_3$) ratio approaches its normal value.

CHART 9

The preceding chart describes complete compensation for an extensive reduction of bicarbonate. Actually, in the presence of large change in bicarbonate, respiratory defense of pH falls considerably short of the mark. The data on this chart describe the extent of compensation found in two instances of extensive reduction of bicarbonate. The first set of measurements of ($B.HCO_3$) and of pH were obtained from a child with chronic nephritis and edema before and after ingestion of the diuretic agent $CaCl_2$. The other measurements are from an infant given hydrochloric acid (in milk) with the purpose of relieving the symptoms of tetany. Ingestion of $CaCl_2$ or of HCl increases the concentration of chloride ion in the plasma with corresponding replacement of bicarbonate. (Diagram 2, chart 6.)

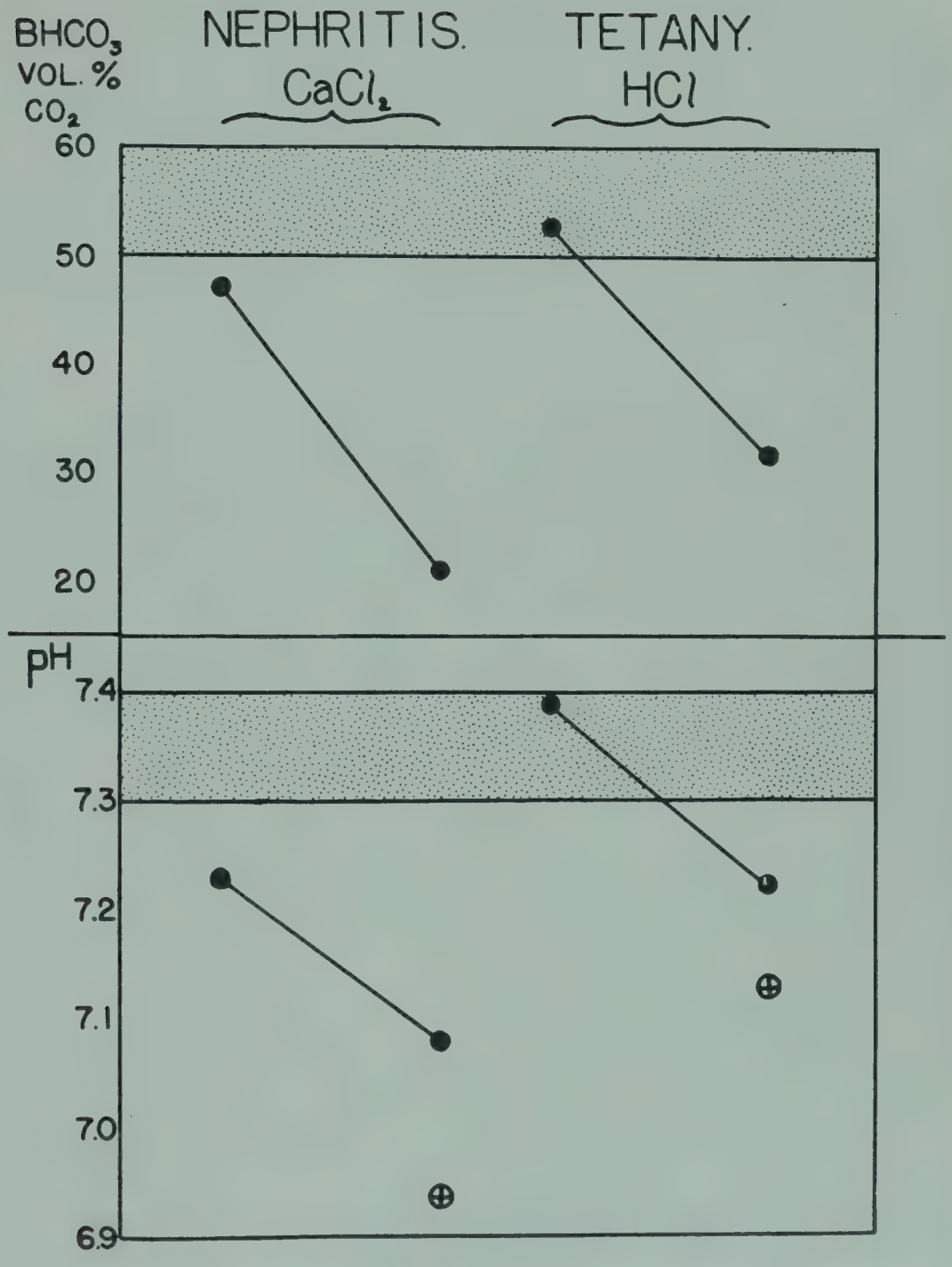

BHCO3 VOL. % CO2
NEPHRITIS. CaCl2
TETANY. HCl
60
50
40
30
20
pH
7.4
7.3
7.2
7.1
7.0
6.9

CHART 9

CHART 9 (Continued)

The points marked by a circle and cross are values for pH as calculated for the reductions of bicarbonate in the absence of any compensating adjustment of carbonic acid. That is, using the Henderson-Hasselbalch equation, $pH = 6.1 - \log \frac{(B.HCO_3)}{(H.HCO_3)}$, the found value for $(B.HCO_3)$ and the normal value for $(H.HCO_3)$, 3 vol. per cent, are taken. The directly determined fall in pH, in these two instances of large $(B.HCO_3)$ reduction, was of about half the extent measured by these calculated values. In other words, respiratory defense of pH was roughly fifty per cent effective.

CHART 10

This chart records measurements obtained by Hartmann from a large series of infants suffering from severe disturbances of gastro-intestinal function. They provide further illustration of the extent of defense of pH in the presence of bicarbonate change. The pH value found for the individual patient is plotted with reference to the accompanying bicarbonate measurement. The average value for $(B.HCO_3)$ in health is, for infants, lower than is found in the plasma of adults and may be taken as 50 vol. per cent. This value prescribes at pH 7.4 a concentration of $H.HCO_3$ of 2.5 volumes per cent. The curved line in the chart defines the position of pH over the range of change in bicarbonate, in the absence of change in carbonic acid, i.e. in the absence of respiratory defense of pH beyond preserving the usual value for $(H.HCO_3)$. The values producing this curve were obtained from the Henderson-Hasselbalch equation on the basis of $(H.HCO_3)$ stationary at 2.5 volumes per cent. In the chart the limits of pH change in health are set at 7.35 and 7.45.

Since the pH values for these infants, lookedat en masse, are seen to drift downward with fall in bicarbonate, incompleteness of respiratory defense is clearly evident. The axis of this drift lies roughly midway between pH 7.4 ("complete compensation") and the curve defining pH in the absence of adjustment of $(H.HCO_3)$, so that statistically respiratory defense of pH may be described as about fifty per cent effective. There is, however, a wide variability in the extent of pH change produced by a given change in $(B.HCO_3)$. In some instances large, and in others small, departure of pH from 7.4 is permitted.

It should be noted that the "no adjustment" curve rests on preservation by the respiratory mechanism of $(H.HCO_3)$ at its usual value. This in itself provides a large initial defense of pH, the extent of which is shown in the next chart.

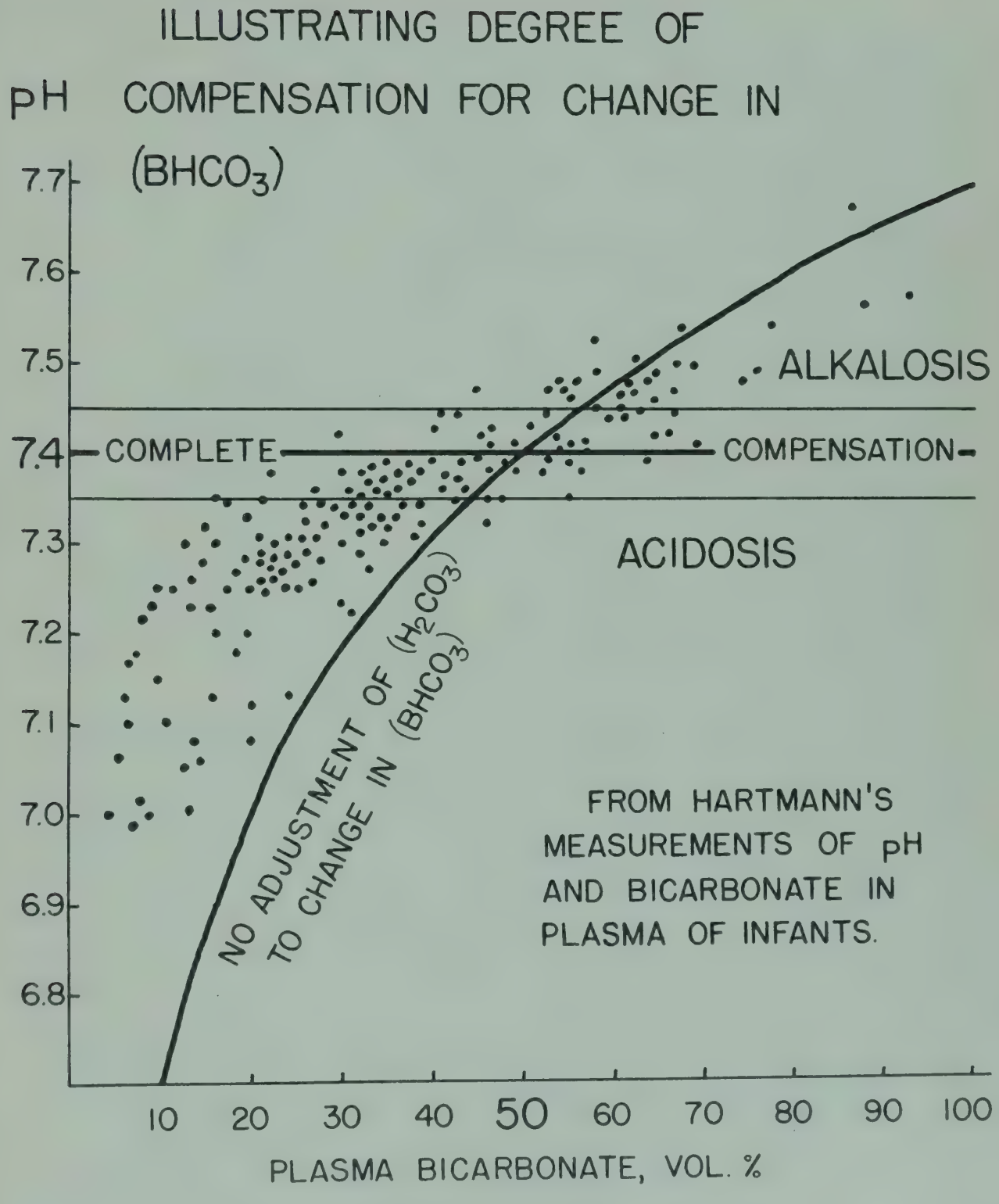

ILLUSTRATING DEGREE OF
pH COMPENSATION FOR CHANGE IN
$(BHCO_3)$
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
ALKALOSIS
COMPLETE
COMPENSATION
ACIDOSIS
NO ADJUSTMENT OF (H_2CO_3) TO CHANGE IN $(BHCO_3)$
FROM HARTMANN'S MEASUREMENTS OF pH AND BICARBONATE IN PLASMA OF INFANTS.
10 20 30 40 50 60 70 80 90 100
PLASMA BICARBONATE, VOL. %

CHART 10

The buffering capacity of the blood plasma may be described as the extent to which it can receive addition of acid or alkali within the limits of reaction change compatible with life. This is measured by change in ($B.HCO_3$) from its usual value, 60 vol. per cent at pH 7.4. The diagrams in the chart record the values for ($B.HCO_3$) over the physiological range of pH as computed by the Henderson-Hasselbalch equation; 1) with reciprocal change in ($H.HCO_3$), in vitro buffering; 2) with ($H.HCO_3$) stationary at its usual value, 3 vol. per cent; 3) with partial adjustment of ($H.HCO_3$). By 50 per cent adjustment is meant change of such extent as to reduce by one-half the movement of pH which a given change in ($B.HCO_3$) would cause in the presence of 3 vol. per cent ($H.HCO_3$).

The diagrams make clear the enormous increase in the buffering capacity of the plasma which respiratory control of ($H.HCO_3$) provides. Without this control, as shown in first diagram, the addition of less than 2 m-eq. of acid per liter brings reaction from pH 7.4 to the physiological boundary and an even small addition of alkali defines buffering capacity in the other direction. In the second diagram respiratory control sustains ($H.HCO_3$) at its usual value. Change in the ratio is thus entirely referable to change in ($B.HCO_3$) which must therefore be of much larger degree to effect a given alteration than is required in the presence of reciprocal change in ($H.HCO_3$). In consequence the steps of bicarbonate change over the physiological range of pH are enormously increased and the buffering capacity of plasma is defined as 16 m-eq/L for acid and 29 m-eq./L for alkali. The further increase in buffering obtained by what may be roughly taken as the usual extent of respiratory adjustment of ($H.HCO_3$) to change in ($B.HCO_3$) is shown in the third diagram. Here more than four-fifths of the normal bicarbonate of plasma may be utilized for the covering of acid addition and, on the other side of pH 7.4, progressively enormous increments of alkali can be received.

The much more extensible defense of the alkaline than of the acid boundary of plasma reaction seen in the diagrams is an interesting feature of carbonic acid-bicarbonate buffering under respiratory control. The intimation which the titration curve of carbonic acid (chart 5) provides, that the position of physiological

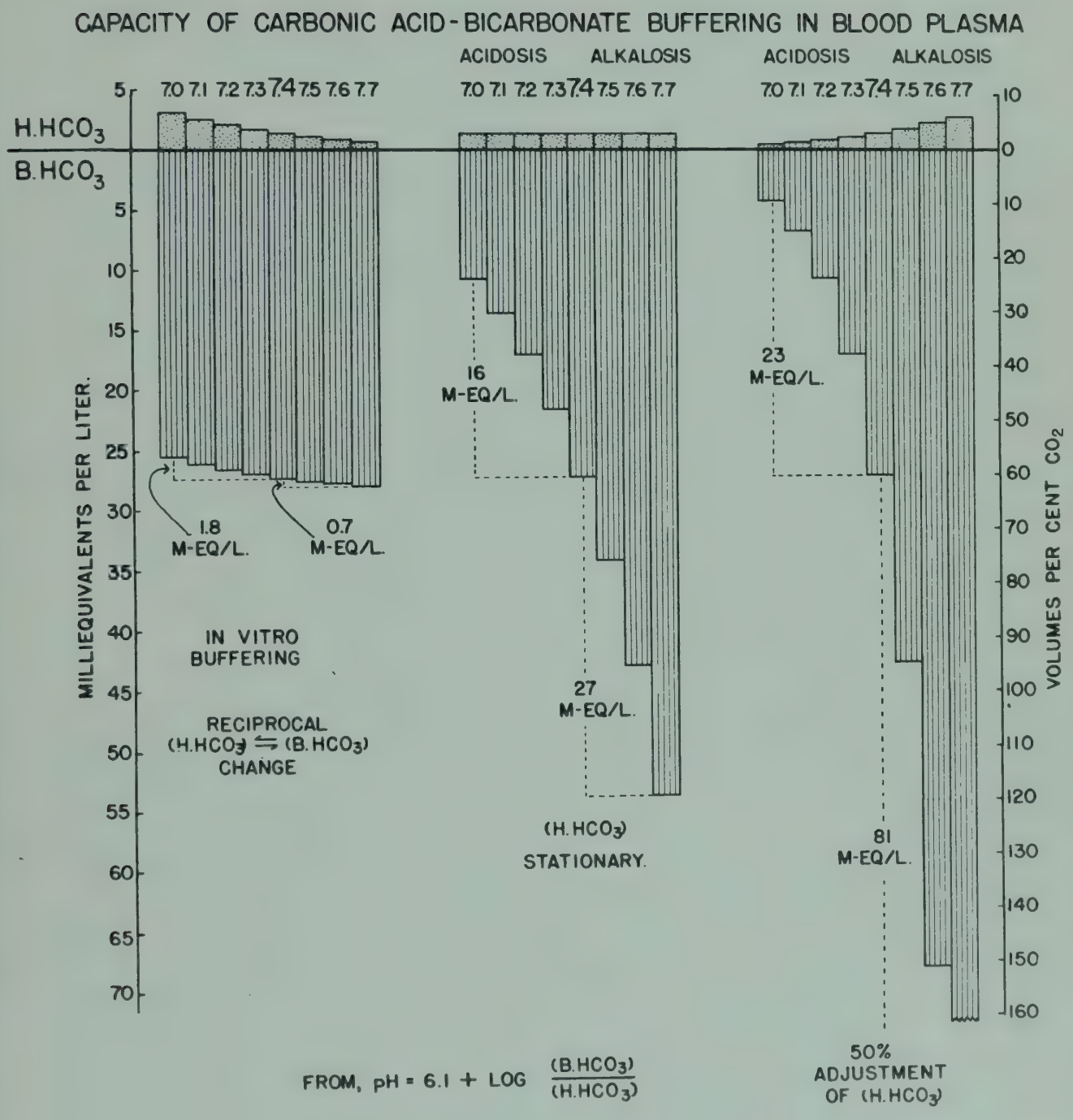

CAPACITY OF CARBONIC ACID-BICARBONATE BUFFERING IN BLOOD PLASMA
ACIDOSIS
ALKALOSIS
ACIDOSIS
ALKALOSIS
7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7
7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7
7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7
H.HCO3
B.HCO3
MILLIEQUIVALENTS PER LITER.
VOLUMES PER CENT CO2
1.8 M-EQ/L.
0.7 M-EQ/L.
IN VITRO BUFFERING
RECIPROCAL (H.HCO3) ⇌ (B.HCO3) CHANGE
16 M-EQ/L.
27 M-EQ/L.
(H.HCO3) STATIONARY.
23 M-EQ/L.
81 M-EQ/L.
50% ADJUSTMENT OF (H.HCO3)
FROM, pH = 6.1 + LOG (B.HCO3)/(H.HCO3)

CHART 11

pH represents an error in biological design, is clearly not sustained. As shown by the diagrams, pH 7.4 is, by the intervention of respiratory control of ($H.HCO_3$), almost ideally defensible.

CHART 12

Conveyance by the blood and removal by the lungs of about two pounds daily of carbonic acid is so skillfully managed that an incorrect concentration in extracellular fluid is a relatively infrequent cause of acidosis or alkalosis. Respiratory control of ($H.HCO_3$) may, however, be disturbed by abnormal circumstances affecting the respiratory center (intracranial lesions, drugs) or the mechanics of lung ventilation as in emphysema.

This chart describes the extent of change in ($H.HCO_3$) within the physiological limits of reaction (in the presence of the usual value for ($B.HCO_3$), 60 vol. per cent). As may be seen a large latitude is permitted. At the acid boundary, ($H.HCO_3$) is more than double, and at the alkaline edge of existence is less than one-half, of the usual value.

Obviously the range of change in ($H.HCO_3$) could be greatly increased or, in other words, the movement of pH for a given change, greatly reduced, by alteration of ($B.HCO_3$) in the direction tending to sustain the normal ratio. By referring to the diagrams in Chart 6, it may be seen that direct addition or removal of $B.HCO_3$ would alter total ionic concentration, and thereby the osmotic value of extracellular fluid. This change in concentration could, however, be obviated by an additional adjustment, a corresponding retention of, or withdrawal of, extracellular water. Another and better method of compensation for an incorrect ($H.HCO_3$) by producing change in ($B.HCO_3$) is suggested by the diagrams in Chart 6. Adjustment of a component of the anion column would cause reciprocal change in (HCO_3') and corresponding change in ($B.HCO_3$) without disturbing total ionic concentration. Obviously, because of its relatively large size, (Cl') would be the suitable anion. Actually compensatory change of (Cl') is observed in situations which have caused a long standing abnormality of ($H.HCO_3$). Illustrations are given in the next chart. Apparently this ingenious mechanism of ($B.HCO_3$)

LIMITS OF CHANGE IN PLASMA ($H.HCO_3$) IN PRESENCE OF NORMAL ($B.HCO_3$)

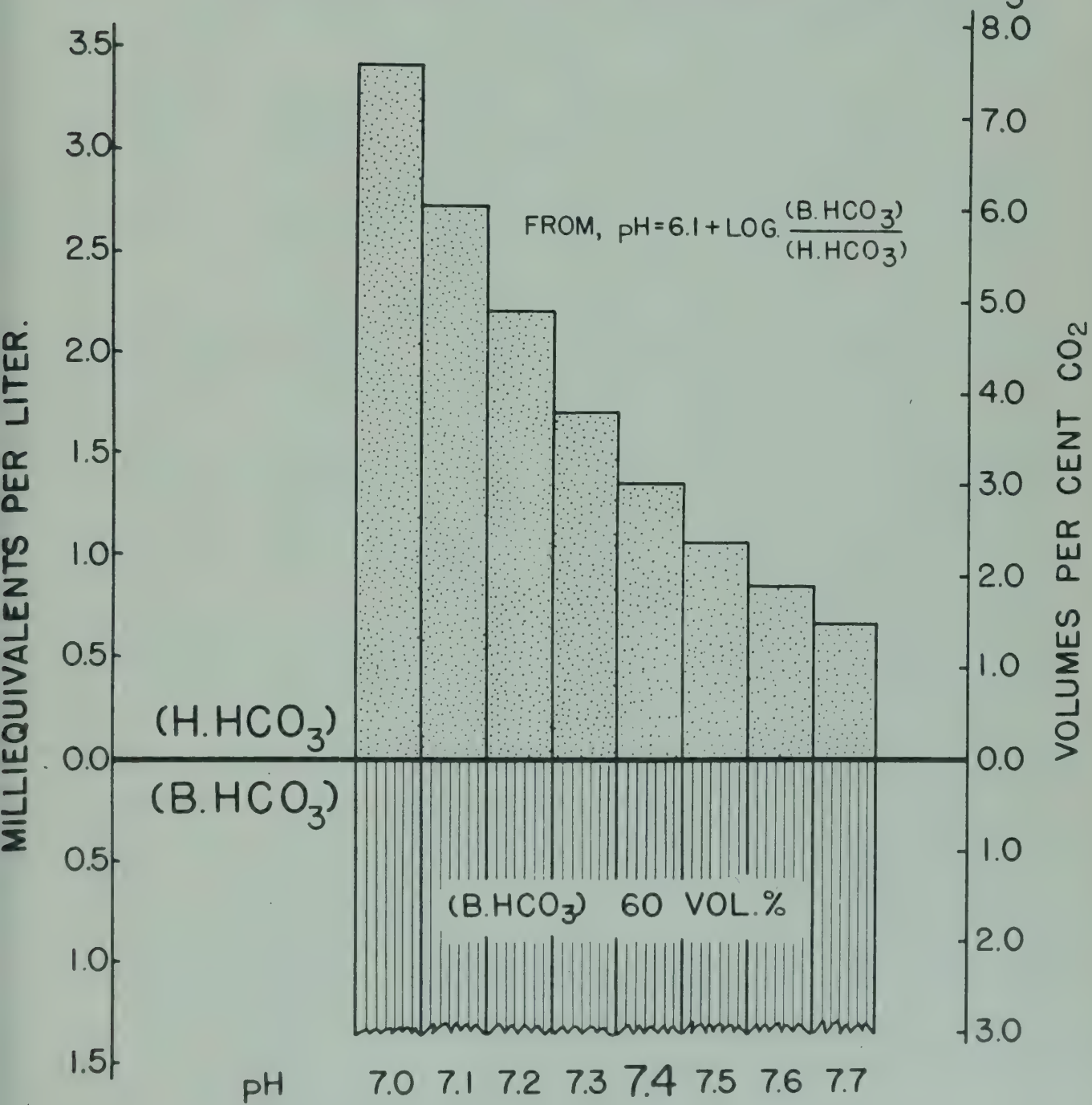


CHART 12

adjustment cannot be set up rapidly. It is not found in the acute situation caused by experimental overbreathing. Here the reduction of ($H.HCO_3$) is offset by direct removal of ($B.HCO_3$) in urine accompanied by diuresis.

CHART 13

The chart illustrates adjustment of ($B.HCO_3$) in the presence of an abnormal ($H.HCO_3$), accomplished by alteration of the usual value for (Cl'). The values for the individual components recorded on the diagrams are milliequivalents per liter.

The first set of diagrams is from a patient with chronic emphysema. Owing to the impairment of ventilation which this condition imposes, CO_2 tension in the residual air is established at a much higher than usual level and ($H.HCO_3$) in the plasma is correspondingly increased. The diagram constructed from the measurements obtained from the patient shows ($B.HCO_3$) extension approximately equivalent to (Cl') recession. With reference to pH, this adjustment of ($B.HCO_3$) in the presence of the increased ($H.HCO_3$) is of such extent as to place the patient's diagram midway between pH 7.4 and pH 7.2 which would have been its position in the absence of change in ($B.HCO_3$). The other set of data are from a patient with chronic hyperventilation (post encephalitic). Here there is a large reduction of ($H.HCO_3$). The patient's diagram shows an increase of (Cl') with resulting reduction of ($B.HCO_3$) of such extent as to more than compensate for the lowered ($H.HCO_3$) so that the diagram lies a bit on the other side of pH 7.4.

(Emphysema data from J.H. Talbott. Hyperventilation data from Peters, Bulger, Eisenman, and Lee.)

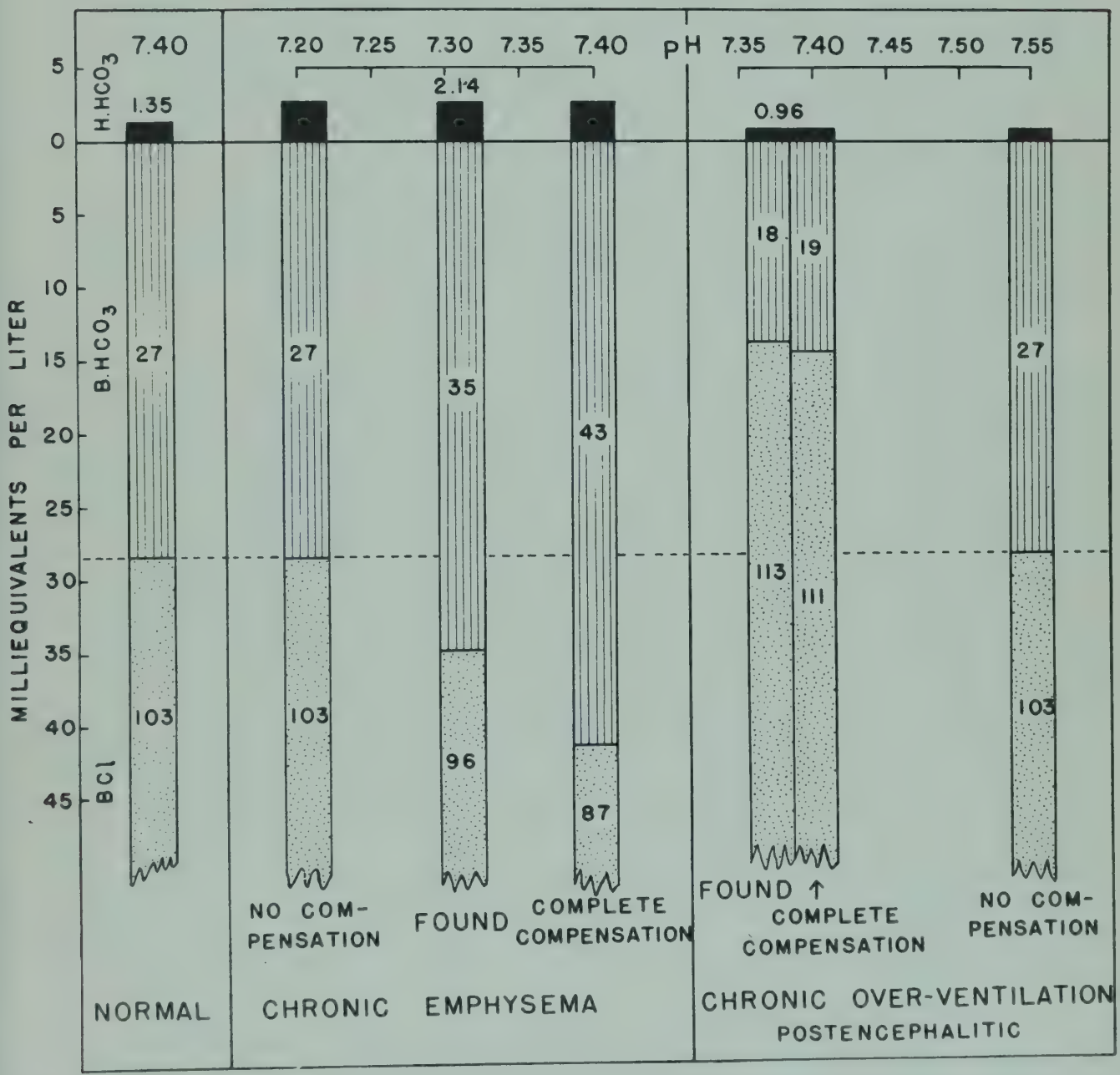

MILLIEQUIVALENTS PER LITER
H.HCO3
B.HCO3
BCl
5
0
5
10
15
20
25
30
35
40
45
7.40
1.35
27
103
7.20
7.25
7.30
7.35
7.40
pH
2.14
27
103
35
96
43
87
NO COM-
PENSATION
FOUND
COMPLETE
COMPENSATION
NORMAL
CHRONIC EMPHYSEMA
7.35
7.40
7.45
7.50
7.55
0.96
18
19
113
111
27
103
FOUND ↑
COMPLETE
COMPENSATION
NO COM-
PENSATION
CHRONIC OVER-VENTILATION
POSTENCEPHALITIC

CHART 13

The osmotic value of extracellular fluid is almost entirely composed of the sum of the concentrations of its ionic components; the non-electrolytes make a relatively very small contribution (Chart 2). An important feature of the total ionic concentration is that it is determined by the sum of the cation values. This is because the adjustable part of the ionic structure is the anion (HCO_3'). Change in other anion values will be offset by reciprocal change in (HCO_3') and so will not alter the total ionic concentration. This may be clearly seen in the diagrams in Chart 6. Since nearly all of the base is sodium, the stability of the osmotic value of extracellular fluid rests almost entirely on the accuracy of renal control of this one component.

Since the intakes of water and sodium have a widely irregular relationship and since renal adjustment requires a considerable time interval, the kidney cannot govern ionic concentration with a sufficient rapidity to meet the requirement for osmotic equality between extracellular and intracellular fluid. There is therefore need for a supplementary mechanism of osmotic adjustment behind the kidney. This mechanism has been brought into view by the experiments of Darrow and Yannet. Its operation rests on the obligatorily extracellular position of sodium and consists simply in the transfer of water across the boundary between extracellular and intracellular fluid in the direction which will produce osmotic equilibrium in the two fluids. This adjustment is quantitatively illustrated by the diagrams in the chart, which describe the extent of volume and concentration changes caused by adding to, or withdrawing from, extracellular fluid 500 milliosmols of NaCl (approximately 15 grams) in the absence of change in the volume of total body water. Volume is recorded on the abscissa and concentration on the ordinate. The diagrams are constructed from the following data:

Body wt., 70 kg.	Ionic conc., 310 m-osM./L. (chart 3)	
Extracell. fl., 70 x .2 (chart 1)	14 L., x 310 =	4340 m-osM.
Intracell. fl., 70 x .5 (chart 1)	35 L., x 310 =	10850 m-osM.
Total body fluid	49 L.	15190 m-osM.

Addition of 500 m-osM. NaCl to extracellular fluid would, without change in volume, increase ionic concentration to 346 m-osM./L. (4340 + 500/14 = 346). By transfer of water to the extracellular compartment, osmotic equilibrium (horizontal broken line)

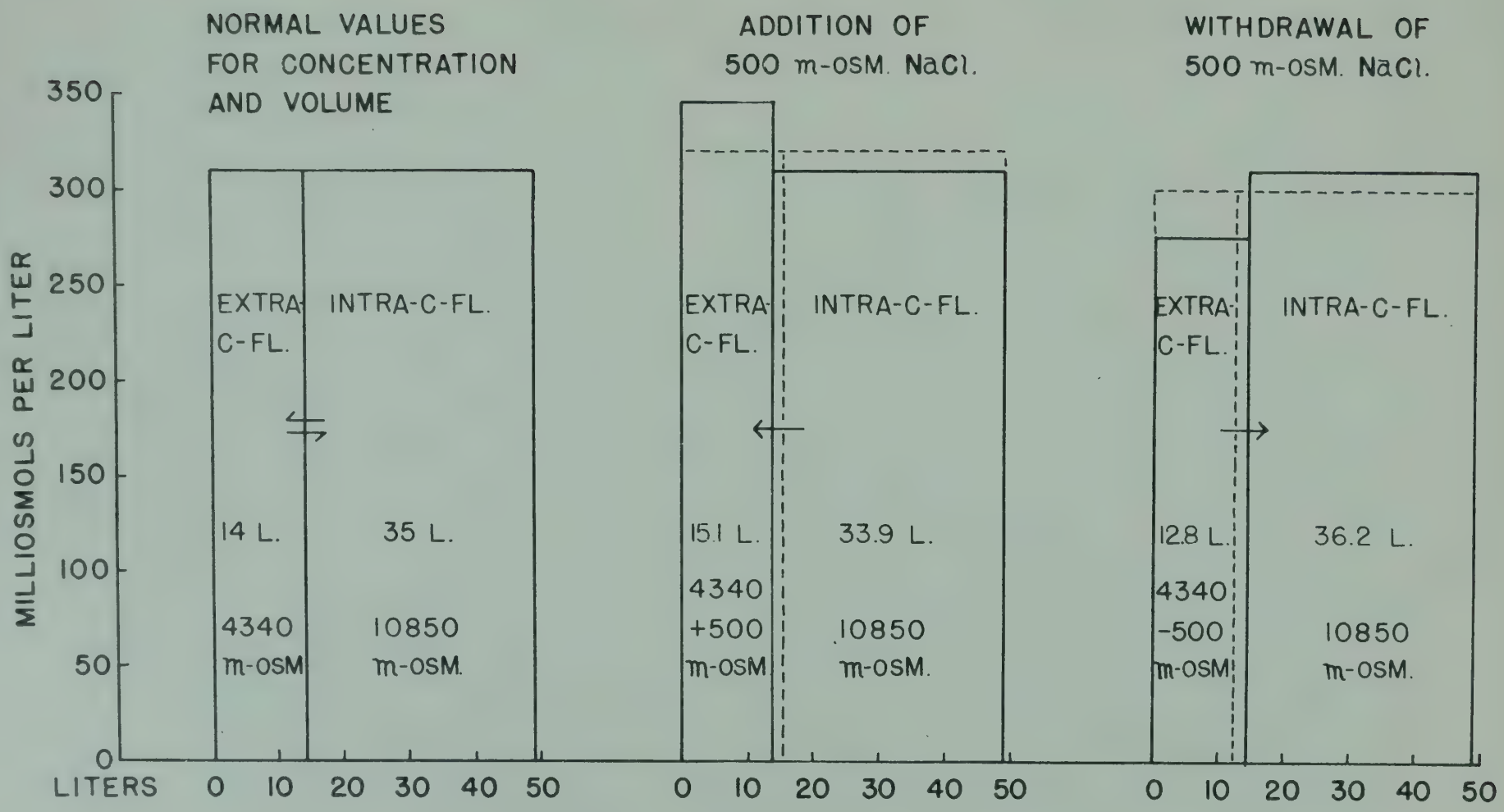


CHART 14 THE DARROW-YANNET DIAGRAM.

is established at an ionic concentration of 320 m-osM./L. (15190 + 500/49 = 320). The change in volume of extracellular fluid (vertical broken line) is from 14 to 15.1 L. (4340 + 500/320 = 15.1). Withdrawal of 500 m-osM. from extracellular fluid would, without volume adjustment, reduce ionic concentration to 274 m-osM./L. (4340 - 500/14 = 274). Equilibrium gained by water transfer to the intracellular compartment raises the ionic concentration level to 300 m-osM./L. (15190 - 500/49 = 300). The incidental reduction of extracellular fluid volume is from 14 to 12.8 L. (4340 - 500/300 = 12.8). By these transfers of about one liter of water, initial change of ionic concentration is reduced by more than two-thirds. Following these immediate osmotic adjustments, renal regulation undertakes to restore the normal ionic concentration and, as this is accomplished, volume dimensions move toward their usual values.

These diagrams provide a large scale illustration of the flexibility of the water-electrolyte system which is necessary even under normal circumstances because of irregularities of intake of sodium (the governing ion of extracellular fluid volume) and of water. It will be understood that total body water is not fixed as in the diagrams and that change in this dimension is also a factor in volume adjustments between extra- and intra-cellular fluid.

CHART 15

This chart will serve to provide a general view of the task of the main organ of regulation of extracellular fluid, the kidney. The urine diagram describes a twenty-four hour specimen obtained from a subject on a usual type of diet. Renal defense of the chemical pattern of the plasma requires the production of a solution of substances widely and variably differing from blood plasma as regards the relative quantities of substances, osmotic value, and reaction. The great width of renal control is shown by the large quantities in urine of substances which are relatively very small components of plasma structure. These are many times concentrated in the urine with respect to their plasma values. The small plasma concentrations minimize encumbrance of the $Na\text{-}Cl\text{-}HCO_3$ frame work on which stability of physical properties rests. This is especially clear in the case of the non-electrolyte and unselectively diffusible substance urea which is serviceable neither in acid-base nor in osmotic mechanisms. Although, as may be seen in the urine diagram, urea composes about one-half of the transport task of extracellular fluid, its conveyance is, by renal efficiency, managed at a relatively extremely small concentration.

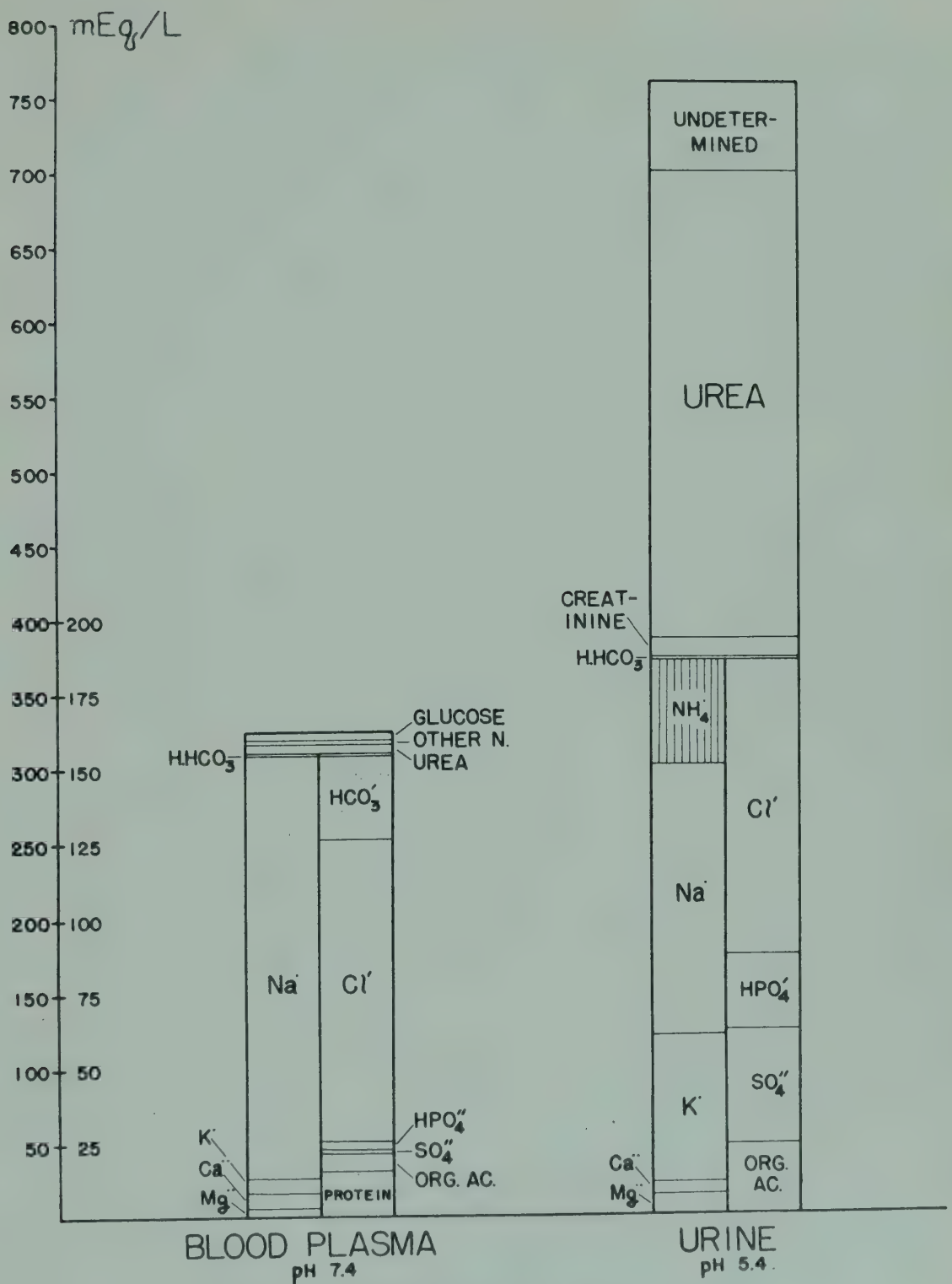

mEq/L
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
200
175
150
125
100
75
50
25
UNDETER-
MINED
UREA
CREAT-
ININE
H.HCO3
NH4
Na
Cl'
HPO4
K
SO4
Ca
Mg
ORG.
AC.
GLUCOSE
OTHER N.
UREA
H.HCO3
HCO3
Na
Cl'
HPO4
SO4
ORG. AC.
K
Ca
Mg
PROTEIN
BLOOD PLASMA
pH 7.4
URINE
pH 5.4

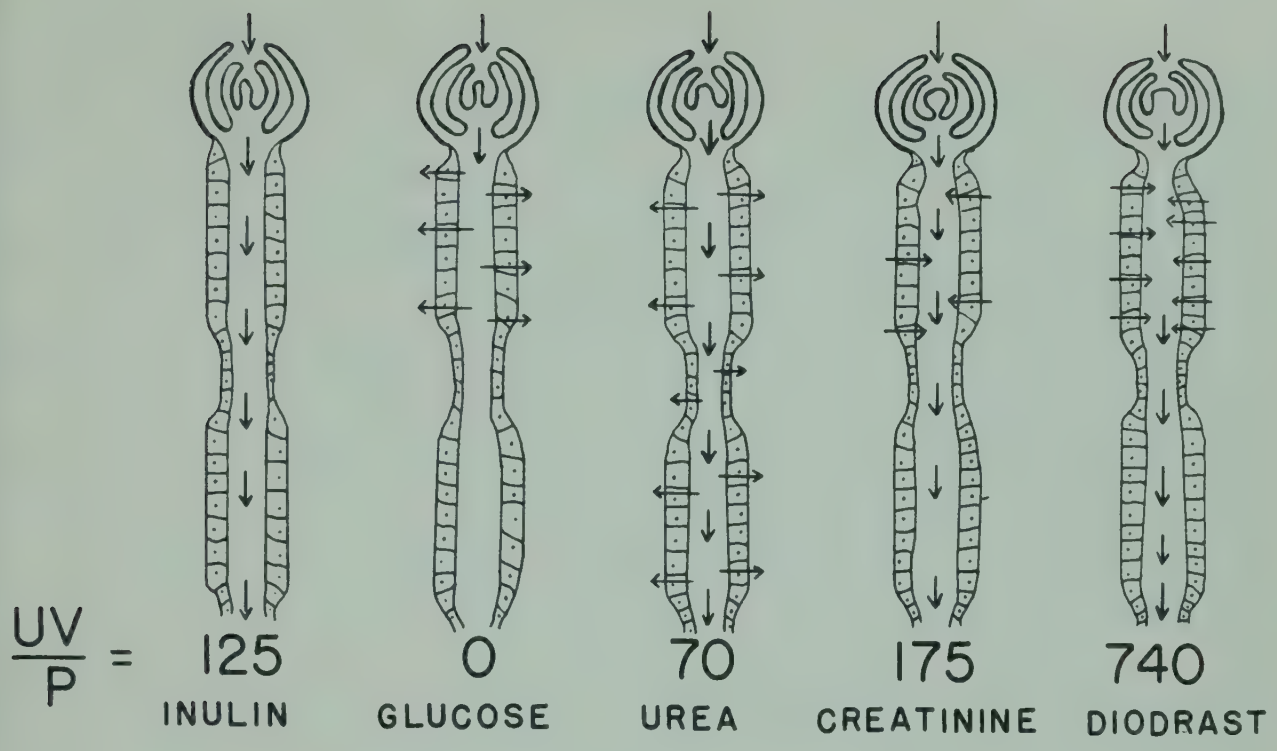
CHART 15

The total concentration of substances in this specimen is more than double that of blood plasma and its reaction, pH 5.2, is widely removed from the fixed plasma value. Several other items of difference may be noted. Three components of plasma, protein, glucose, and bicarbonate, are not found in the urine. Protein does not enter glomerular filtrate in health. Glucose is completely reabsorbed from it. Bicarbonate in urine is a function of pH and is not found to an appreciable extent in urine of this degree of acidity (Chart 24). Urine contains the base ammonium which is (probably) not present in plasma. The only substance which is found at approximately the same concentration in both fluids is carbonic acid.

CHART 16

The general features of renal control of the composition of blood plasma have been brought into view. The dauntless ingenuity of A. N. Richards has provided direct evidence that plasma filtration by the glomerulus is a simple physical process. An additional process of direct tubular excretion of certain substances has been established. It is nevertheless clear that renal regulation consists essentially in selective reabsorption of water and substances from glomerular filtrate by the tubule cells.

Although the mechanisms of selective reabsorption have not been uncovered, the outside dimensions of the renal process have been defined by the so-called clearance method of study. The conception and development of the clearance measurement, which is of great usefulness clinically and to renal physiologists, rests chiefly on the work of Addis and Barnett, and of Van Slyke. Obviously clearance does not imply complete removal of a substance from plasma. Only a fraction of the plasma is filtered and, in the case of urea, for instance, there is a large return from filtrate to plasma across the tubule cells. Clearance is an arbitrary, but quantitatively valid, statement which refers the amount of a substance found in the urine over a unit of time to the volume of plasma which it would occupy at the existing plasma concentration. This volume may be computed from the equation $UV/P = C$, in which U is concentration of the substance in urine, P its concentration in plasma, and V the volume of urine secreted per minute. If there is direct proportionality between the plasma concentration of a substance, P, and the rate of its removal, UV, clearance will have for the individual, a constant value and will serve as a measurement of the capacity of the kidney in terms of plasma dealt with over a unit of time. This capacity is determined by the total number of functionally active



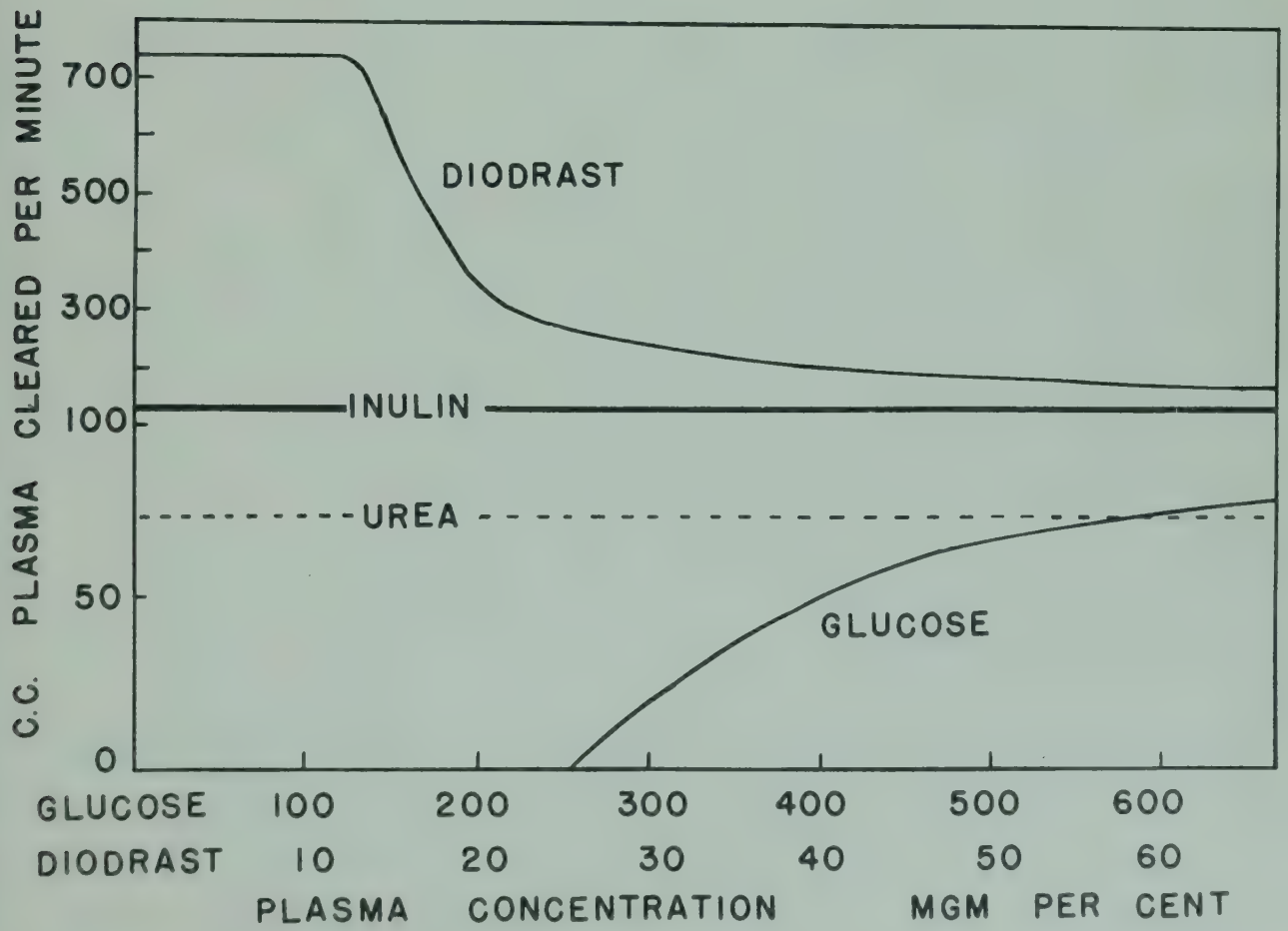


CHART 16 FROM HOMER SMITH

renal units or nephrons. Reduction of clearance therefore measures a loss of renal equipment. This does not, however, imply a reduction of excretory capacity. The "smaller" kidney of Brights disease is able to excrete urea, for instance, as rapidly as the kidney in health by the simple device of an increase in plasma concentration which produces correspondingly increased removal of urea from the reduced volume of plasma dealt with over a unit of time. P:UV proportionality is exhibited by a number of chemically inert non-threshold substances. A few of these are normal components of plasma; others are foreign substances. Since the concentrations of the most prominent components of plasma, the electrolytes, must be held closely stationary, a linear P:UV relationship would not be expected. Their clearance values are found to vary widely with change in the rate of intake and therefore have no utility as a measurement of overall renal capacity.

The clearance values (established for an adult of average size) for several substances, which are especially serviceable in this method of study, are recorded in the chart. The values differ and the reason for this is indicated in the diagrams. The substance inulin is believed to be removed from plasma exclusively by the process of glomerular filtration. The value found for inulin clearance therefore incidentally defines an important dimension of the renal process, the rate of glomerular filtration, as 125 cc. per minute. Under normal circumstances glucose is completely reabsorbed from glomerular filtrate and so has a clearance value of zero. Following ingestion of creatinine, the value found for its clearance is 175 cc. per min. Since, according to inulin, the limit of clearance by the process of glomerular filtration is 125 cc. per min. (the volume of plasma filtered), the additional 50 cc. of plasma must have been cleared by direct tubular excretion. Recent studies without administration of creatinine have produced measurements approximating the inulin value and therefore suggest that clearance of endogenous creatinine is accomplished entirely by glomerular filtration. The clearance value for urea is below that for inulin because of return to the plasma of a large part of the urea in glomerular filtrate. According to indirect evidence, urea is not actively reabsorbed but crosses the tubule cells by a process of passive diffusion. For the substance diodrast, the enormous clearance value of 740 cc. per minute has been found, which except for 125 cc. (glomerular clearance), must be accounted for by tubular excretion. This clearance of diodrast is regarded as ultimate in renal excretory achievement; a complete removal from the plasma during its passage through the kidney. On this premise it defines another basal dimension of renal activity, the volume flow of blood plasma.

Comparison of this value for plasma flow with the value for glomerular filtration defined by inulin clearance produces an additional datum of interest; about one-fifth of the plasma entering the kidney is filtered by the glomeruli.

The direct proportionality between the plasma concentration of a substance and the rate of its removal in urine on which a stationary clearance value depends, may be expected to hold, regardless of increase in plasma level, for substances which are dealt with by "passive" physical processes. When, however, "activity" of the tubule cells is involved, a limit to the capacity of the process of transfer may be expected, beyond which, rate of tubular absorption or excretion cannot follow rise in plasma concentration. This is clearly illustrated by the lower diagram in the chart. The clearance values for inulin and urea are stationary at all plasma levels. With increase in the concentration of glucose in plasma, a level is reached which marks the limit of the capacity of the tubule cells to reabsorb glucose from glomerular filtrate and a progressively increasing remainder is found in the urine. Clearance of diodrast is stationary only over low levels of plasma concentration. With further increase, clearance falls rapidly and extensively, indicating that the maximal capacity of the tubule cells to excrete diodrast has been passed. According to Homer Smith, the plasma concentration of glucose beyond which it enters the urine may be taken as 256 mg/100 cc. (arterial plasma). Using the standard volume for glomerular filtration, the maximal rate of glucose absorption by the tubule cells is 256 x 1.25 = 320 mg/min. A value of 57 mg/min. has been established as the maximal excretory capacity for diodrast. Homer Smith and his associates have made ingenious application of the differing ways in which the kidney deals with inulin, glucose and diodrast to appraisement of the extent and character of structural damage in renal disease. They designate maximal glucose absorption, glucose Tm and maximal diodrast excretion, diodrast Tm. To very briefly indicate the scheme of this method of study: by reference to standard values; glucose Tm measures intact nephrons, since both glomerulus and tubule are required; diodrast Tm measures tubular excretory function, and since the glomerulus is not required, diodrast Tm minus glucose Tm measures aglomerular tubules; and since inulin needs only glomeruli, inulin clearance minus glucose Tm measures functionless tubules with intact glomeruli.

The filtration-reabsorption method of renal control has rather startling quantitative implications. The rate of glomerular filtration defined by inulin clearance, 125 cc. per minute, produces over the twenty-four hour period a volume of 180 liters. Since urine volume is usually not more than two liters, almost all of the water of the filtrate must be reabsorbed by the tubule cells, also, since only the surpluses of components of the ionic structure of the plasma are removed in urine, the greater part of these materials must be returned to the plasma from glomerular filtrate. This aspect of control of the electrolytes is quantitatively described by the estimations of filtration and of reabsorption given in the table below. These are derived from the quantities found in a twenty-four hour urine specimen from a healthy adult on a usual dietary, assuming normal concentrations in plasma leaving the kidney and a glomerular filtrate volume of 180 liters.

	A Plasma Concentration	B Filtered (A x 180)	C Found in urine	D Reabsorbed (B - C)	Per Cent Reabsorbed D/B
	mM/L	mM	mM		
Na	142	25560	111	25449	99.6
Cl	103	18540	119	18421	99.4
K	5	900	60	840	93.4
HPO_4	1	180	30	150	83.4
SO_4	0.5	90	23	67	74.4

Expressed in the more familiar term of weight, the quantities of the two large components of plasma, Na and Cl, amount together to more than a kilogram. The volume of the specimen was 1.2 liters. Reabsorption of water from the filtrate was therefore 178.8 liters (99.4%). The magnitude of the reabsorption task of the tubule cells is apparent in the table and in the chart which describes the filtration-reabsorption ratios.

The volume flow of plasma through the kidney, as defined by the diodrast clearance value, 740 cc/min., is also astonishingly large. This quantity of plasma corresponds to about 1300 cc. of blood which is more than one-quarter of the total cardiac output of the heart under basal physiological conditions.

These definitions of the rate of glomerular filtration and of plasma flow which the clearance method of study has produced make impressively clear the rapidity of operation of the renal process which maintenance of the integrity of extracellular fluid requires.

PROPORTIONS OF COMPONENTS OF GLOMERULAR FILTRATE REABSORBED □ AND EXCRETED IN URINE ■

CHART 17A

A measurement of the total output of substances by the kidney over a unit of time, and of the quantity of water which their removal requires, can be derived from determination of the freezing point depression of the urine. Dividing degrees of freezing point depression by 1.86 defines solute concentration as osmoles per liter. Multiplying osmolar concentration by cubic centimeters of urine produces a measurement of total solutes as milliosmoles. The average maximal for the kidneys' ability to concentrate solutes in urine is 1.4 osM/L. Dividing the value found for total solute output by 1.4 defines the minimal renal water requirement. For example:

24 hr. Urine volume, 1240 cc. Freezing point depression, -1.19°.
1.19/1.86 = 0.64 osmoles per liter. Solute concentration.
1240 x .064 = 794 milliosmoles. Total solute output.
794/1.4 = 566 cc. Minimal Urine Volume.

The solute output which derives from an ordinary dietary is in the neighborhood of 1200 milliosmoles per 24 hours. For a food intake low in protein and salt, and high in carbohydrates it may fall as low as 200. Urine volume required for removal of various solute loads across the range of solute concentration, above that of glomerular filtrate, is shown in the chart. It will be seen that, if maximal concentration is reached, minimal water expenditure by the kidney will range from 150 to 900 cc. according to the quantity of solutes claiming removal.

It is physiologically interesting that the curves describe a diminishing water gain with increase of concentration. At the concentration of glomerular filtrate 4 liters of water are required to remove 1200 milliosmoles of solutes. By moving concentration only as far as 0.6 osM/L, the water expenditure is reduced to 2 liters. To bring it down to 1 liter, concentration must be carried to 1.2 osM/L, and beyond this point water gain, with increase of concentration, becomes nearly negligible. So it may be observed that, although maximal concentration is presumably defined by a limit to the kidney's ability to do osmotic work, it produces a conservation of water which is very near the theoretically attainable mark.

The chart illustrates the clinical utility of a measurement of total solute output. This measurement provides definition of the quantity of water which the kidney requires in a given situation for the removal of solutes at a usual or at a maximal concentration, or at a greatly lowered concentration imposed by disease.

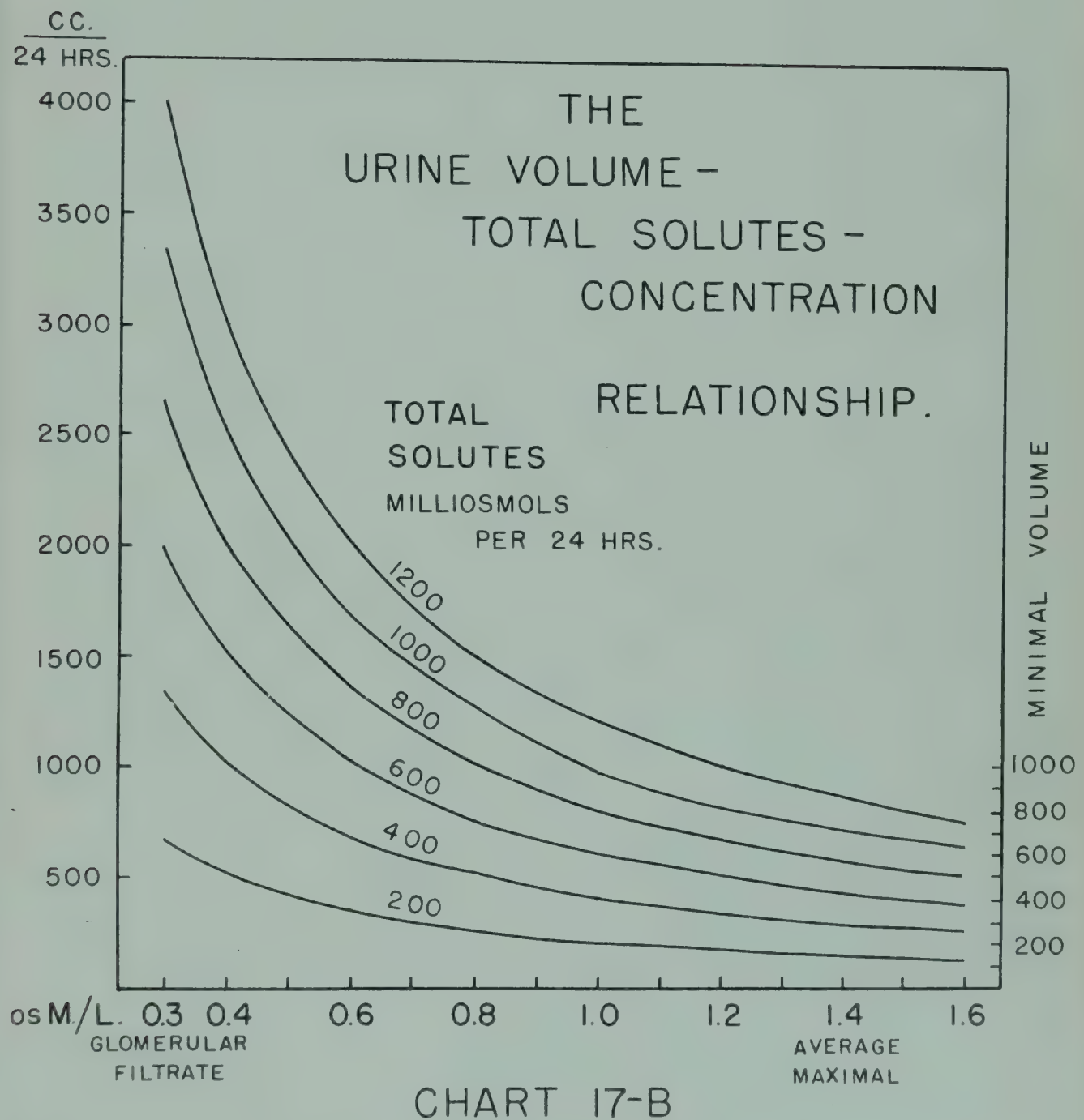

CC.
24 HRS.
4000
3500
3000
2500
2000
1500
1000
500
THE
URINE VOLUME -
TOTAL SOLUTES -
CONCENTRATION
RELATIONSHIP.
TOTAL
SOLUTES
MILLIOSMOLS
PER 24 HRS.
1200
1000
800
600
400
200
MINIMAL VOLUME
1000
800
600
400
200
osM/L. 0.3 0.4 0.6 0.8 1.0 1.2 1.4 1.6
GLOMERULAR
FILTRATE
AVERAGE
MAXIMAL

CHART 17-B

In the equation for the computation of clearance, UV/P = C (Chart 16), UV measures load (L); i.e., the quantity of the substance claiming removal in urine over a unit of time. For substances whose plasma concentrations are permitted to move in proportion to load, clearance has a stationary value. For the foreign substance inulin, clearance measures the volume of glomerular filtrate (F). For this substance the equation may therefore be written L/P = F, or in order to present the relation of plasma concentration to load and volume of filtrate, L/F = P. A normal component of plasma, urea, is also removed entirely by glomerular filtration. A large part of the urea filtered goes back to the plasma across the tubule cells by a passive process known as "back diffusion". Since inulin clearance measures glomerular filtrate, the extent to which urea in the filtrate is removed in urine may be defined by comparing the normal clearances of urea and inulin (Chart 16); 75/125 = 0.6. In other words, 60% of the volume of filtrate is effective in the removal of urea from plasma. The equation describing the relation of plasma concentration of urea to load and the filtration capacity of the kidney is, therefore, L/F x 0.6 = P.

The chart is constructed on these premises. The values taken for the 24 hr. loads of urea derive from small, usual, and large protein intakes, approximately 40, 80, and 120 gm. respectively. Since the protein intake requirement for nitrogen balance is, for an adult, about 40 gm., the small urea load, 200 milliosmols, may be regarded as physiologically minimal. The curves record the rise in plasma concentration for the several loads as the volume of glomerular filtrate falls progressively below its normal value.

The filtrate volume-plasma concentration relation produces, for given loads, the hyperbolic curves recorded in the chart; with progressive reduction of F, P rises at first gradually and then rapidly. The chart explains the clinical observation that P is not found appreciably above the "normal range" until filtrate volume has been reduced by more than one-half of its normal value. It is, however, evident that the "normal range" of P for a normal volume of filtrate is produced by variation of load. It is therefore understandable that the small load (200 millimols) removed in one-half the normal volume of filtrate will produce the same plasma concentration as the usual load (400 millimols) removed in a normal filtrate volume. Interpretation of plasma concentration in relation to filtration capacity thus requires definition of load. If, however, both P and L are measured, F x 0.6 (the effective volume of glomerular filtrate which corresponds with the volume of plasma cleared

of urea) is defined. Since clearance has a linear relation to total filtrate, regardless of load, it is as shown by the chart a much better index of filtration capacity than is plasma concentration, especially over the early stage of reduction of filtrate volume.

The main purpose of the chart is to make it clear that the concentration of urea in plasma is the concentration required in glomerular filtrate for removal of the daily urea load. With reduction of filtration capacity there is proportionate increase of urea concentration in plasma and filtrate which permits successfulremoval of the load. This is a simple automatic adjustment produced by constriction of filtrate volume. The high levels of plasma urea found in Bright's disease are therefore incorrectly described as "retention" in the sense of renal inability to remove urea. Although azotemia serves as an index of renal damage, it is also to be regarded as a beneficient event which enables the diseased kidney to remove urea as rapidly and completely as the healthy kidney. As shown in the chart, the plasma urea level required for removal of the daily load in a small volume of filtrate can be extensively reduced by lowering load to the physiological minimal.

The derivation (above) of effective filtrate as F x 0.6 rests on the normal value, 75cc/min. for maximal urea clearance which requires a urine flow above 2cc/min. The normal value for so-called standard clearance is 50cc/min. and is based on a urine flow of 1cc/min., or 1440cc/24 hrs. which is about the usual rate of urine secretion. With a clearance of 50cc/min., effective filtrate is F x 0.4, i.e. at the slower rate of urine flow, 60% of the urea in filtrate returns to plasma instead of 40% found for maximal clearance. In the chart, values for P in relation to L for normal F, computed on the basis of standard clearance, are shown by the circles with dot. If the limitation of back diffusion of urea to 40% of urea filtered (maximal clearance) is the result of twice the usual rate of urine flow, then reduction of filtration capacity by one-half should double the rate of flow per nephron for a usual water load and so meet the requirement for maximal clearance. Reduction of glomerular capacity should, then, incidentally produce maximal efficiency in removal of urea from filtrate without increase of the usual water load.

The data presented in the chart rest on the assumption that the 60:40 partition of urea filtered between urine and plasma (by back diffusion) defined in health by maximal urea clearance obtains regularly in renal disease. Although the accuracy of this

assumption is not established, it must be used as an approximation in interpretation of the urea clearance measurement. As a corollary, the volume of glomerular filtrate can be defined by multiplying a measurement of maximal urea clearance by 1.67. This factor derives from the normal clearance values for inulin and urea; 125/75 = 1.67.

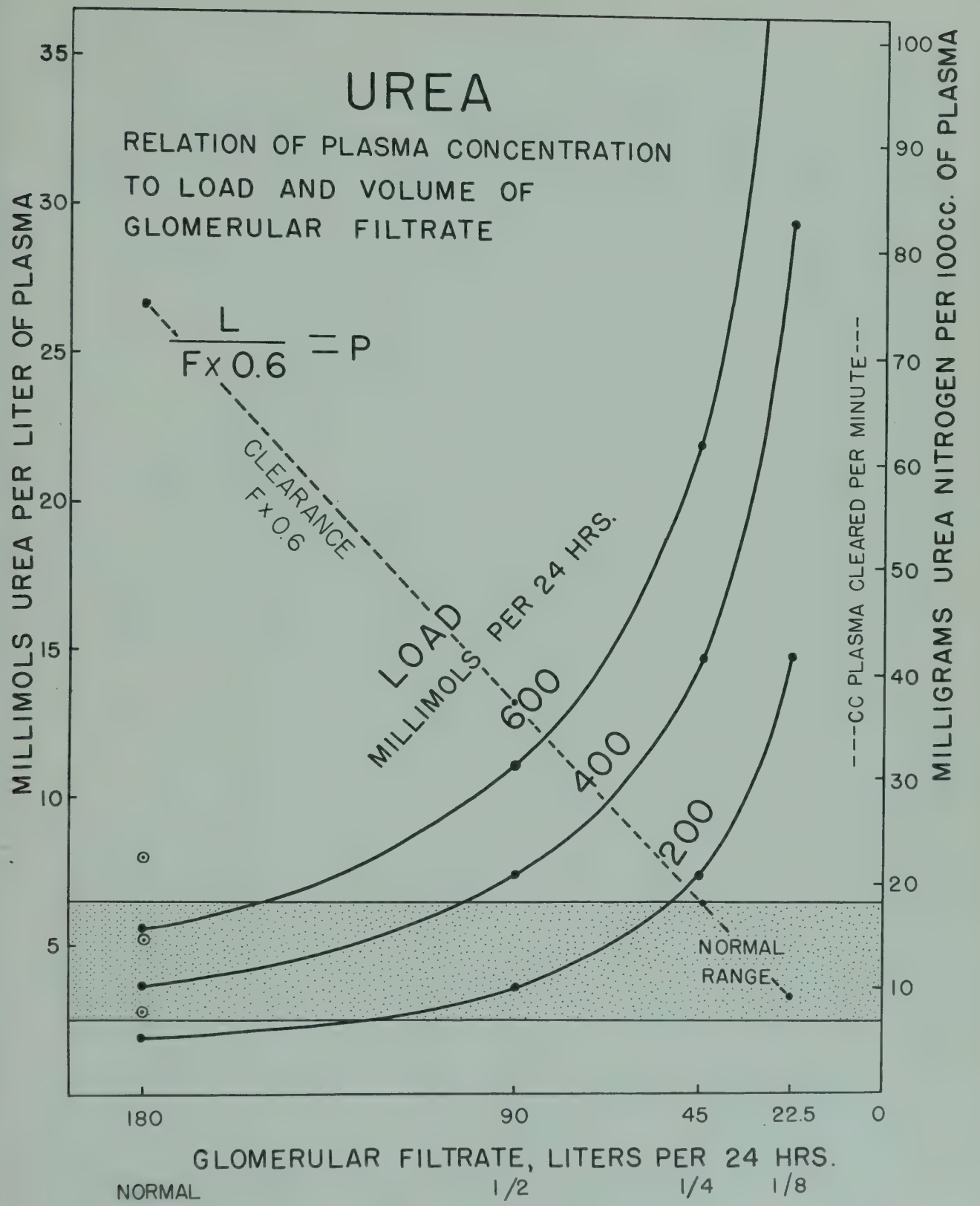

UREA
RELATION OF PLASMA CONCENTRATION TO LOAD AND VOLUME OF GLOMERULAR FILTRATE
L / F x 0.6 = P
CLEARANCE F x 0.6
LOAD MILLIMOLS PER 24 HRS.
600
400
200
NORMAL RANGE
MILLIMOLS UREA PER LITER OF PLASMA
MILLIGRAMS UREA NITROGEN PER 100cc. OF PLASMA
---CC PLASMA CLEARED PER MINUTE---
35
30
25
20
15
10
5
100
90
80
70
60
50
40
30
20
10
180
90
45
22.5
0
GLOMERULAR FILTRATE, LITERS PER 24 HRS.
NORMAL
1/2
1/4
1/8

CHART 17-C

CHART 17-D

The integrity of the ionic structure of blood plasma requires that the concentration of its individual components be held at closely stationary values. This is accomplished by regulated reabsorption from glomerular filtrate. An initial requirement for preservation of a prescribed level for a plasma component is that it must be set well above the concentrations which a normal volume of glomerular filtrate and a usual range of load would command. The plasma electrolytes are found to have wide margins of safety which permit their preservation in the presence of extensive reduction of filtration volume. This is illustrated in the chart by the P values for HPO_4 produced by L/F. Not until filtrate has been reduced below one-quarter of its normal value does the usual HPO_4 load produce a concentration above the normal plasma level. The chart explains the absence of rise in plasma HPO_4 in the early stages of renal disease. It may be noted that the eventual elevation of P is not progressive for a given reduction of F; it remains at the position required for removal of L in F. Rise in P is not, however, as in the case of urea, a harmless event since it disturbs the normal electrolyte structure of the plasma. The therapeutic efficacy of reduction of load is shown in the chart.

CHART 17-E

The width of security of the plasma concentration of an electrolyte can be very simply defined by comparing the usual load with the quantity filtered per 24 hrs.; P x F. As shown in the table, the quantity of HPO_4 filtered daily in a normal volume of filtrate is 4-1/2 times the usual load. Not until filtrate is reduced to 20% of normal volume does the quantity of HPO_4 filtered at the normal plasma concentration fall below the usual load. In other words, until this point of reduction of F is reached, L will be removed without elevation of P above the normal level. With a usual intake of K, a normal plasma concentration will be preserved until filtrate volume falls below 20% of normal. These statements require the reservation that they apply only to the relation of plasma concentration to filtration capacity. Since normal plasma concentrations of the electrolytes are sustained by regulated reabsorption from glomerular filtrate, incorrect concentrations will be caused by error in this process.

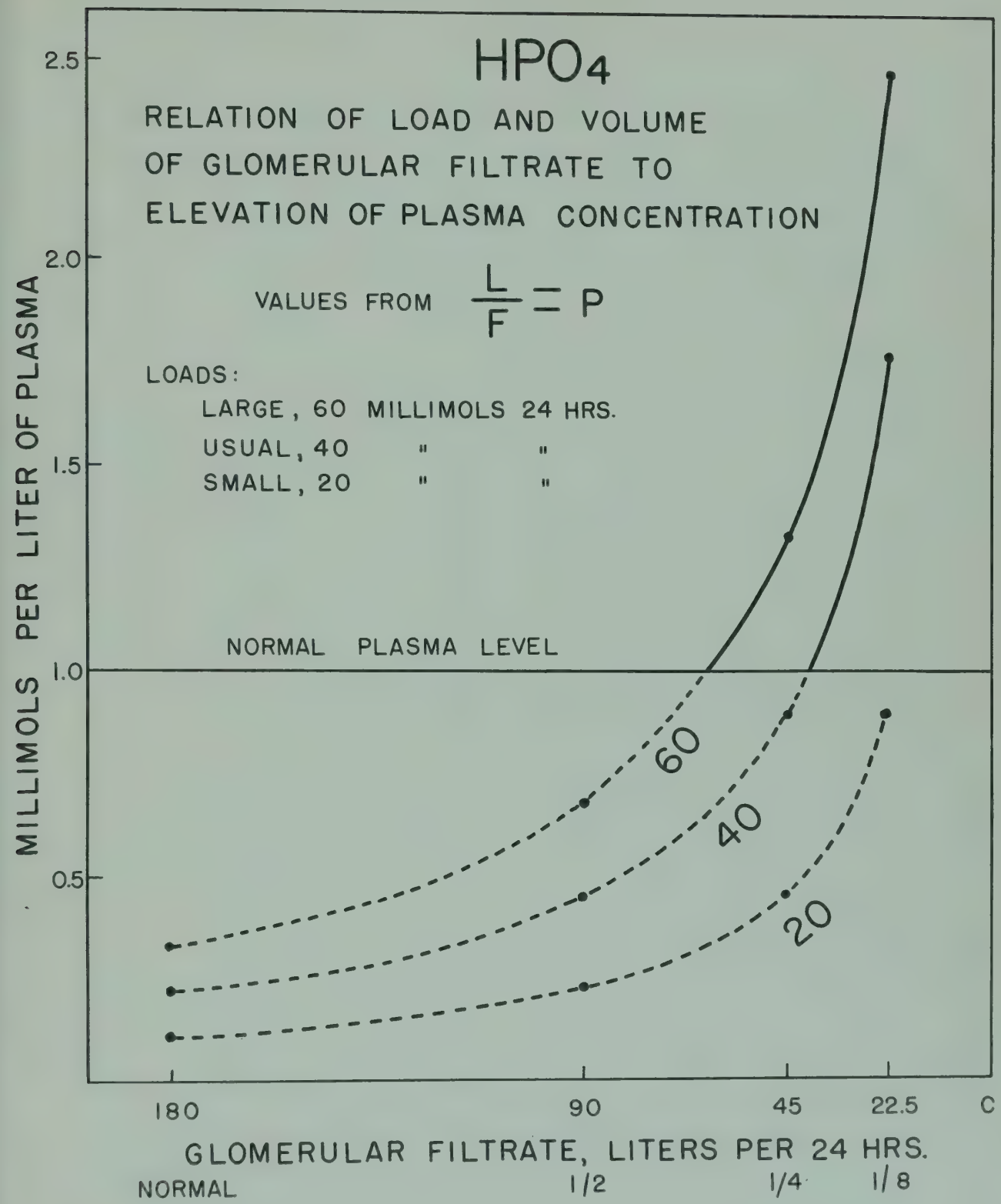

HPO4
RELATION OF LOAD AND VOLUME
OF GLOMERULAR FILTRATE TO
ELEVATION OF PLASMA CONCENTRATION
VALUES FROM L/F = P
LOADS:
LARGE, 60 MILLIMOLS 24 HRS.
USUAL, 40 " "
SMALL, 20 " "
NORMAL PLASMA LEVEL
MILLIMOLS PER LITER OF PLASMA
2.5
2.0
1.5
1.0
0.5
60
40
20
180
90
45
22.5
C
GLOMERULAR FILTRATE, LITERS PER 24 HRS.
NORMAL
1/2
1/4
1/8

CHART 17-D

As shown by the data for Cl in the table, the quantities of Cl and Na filtered daily are, owing to their large plasma concentrations, enormously greater than load, even when filtration capacity is reduced below 10% of normal. It is evident that a rise in plasma concentration of Cl or Na cannot result from deficient filtration but must be referred to inaccuracy of tubular reabsorption.

CHART 17-F

The construction of urine from glomerular filtrate of plasma requires osmotic work. This work is applied to the production of concentrations of the individual urine solutes which differ widely from their respective plasma levels. As shown in Chart 15, under usual circumstances as regards intake and urine volume, the two large components of the electrolyte structure of plasma, Na and Cl, are removed in urine at concentrations below their plasma values. All of the other urine solutes, except carbonic acid, are found at concentrations more or less extensively above plasma levels; the concentration of urea which composes about one-third of the total solute output is many times its small plasma value.

Effects of reduction of renal capacity for osmotic work can be derived from consideration of the relation of urine volume to the work requirement for removal of usual 24-hr. loads of urea and of Na shown in the chart. The lowering of concentrations produced by increase in volume brings urea toward its plasma value but causes further departure of (Na) below its plasma level. With increase in volume, the work requirement is therefore lowered for urea but is raised for Na. When available energy falls below the requirement for removal of urea in a usual urine volume, increase in volume to the extent which will lower the work requirement sufficiently to permit removal of the urea load is osmotically compulsory. The initial event produced by extensive reduction of the kidney's osmotic work capacity is, then, obligatory polyuria. The increase in volume established by urea produces the requirement for proportionate reduction of the concentration of Na. To such extent as the increased work required for this reduction is beyond available energy, Na will be removed in urine at concentrations above the values required for intake-outgo balance and deficits will result unless covered by increased intake. These relations also hold for removal of Cl in urine.

DAILY FILTRATION of HPO_4, K, and Cl

GLOMERULAR FILTRATE		HPO_4 1 m.mol/L	K 5 m.mol/L	Cl 100 m.mol/L
Liters/24 hrs.		m. mol 24 hrs.	m.mol/24 hrs.	m.mol / 24 hrs.
NORMAL	180	180	900	18000
70%	126	126	630	12600
50%	90	90	450	9000
40%	72	72	360	7200
30%	54	54	270	5400
20%	36	36	180	3600
10%	18	18	90	1800
LOAD, m.mol/24 hrs:				
Small,		20	50	50
Average,		40	150	150
Large,		60	200	200

CHART 17-E

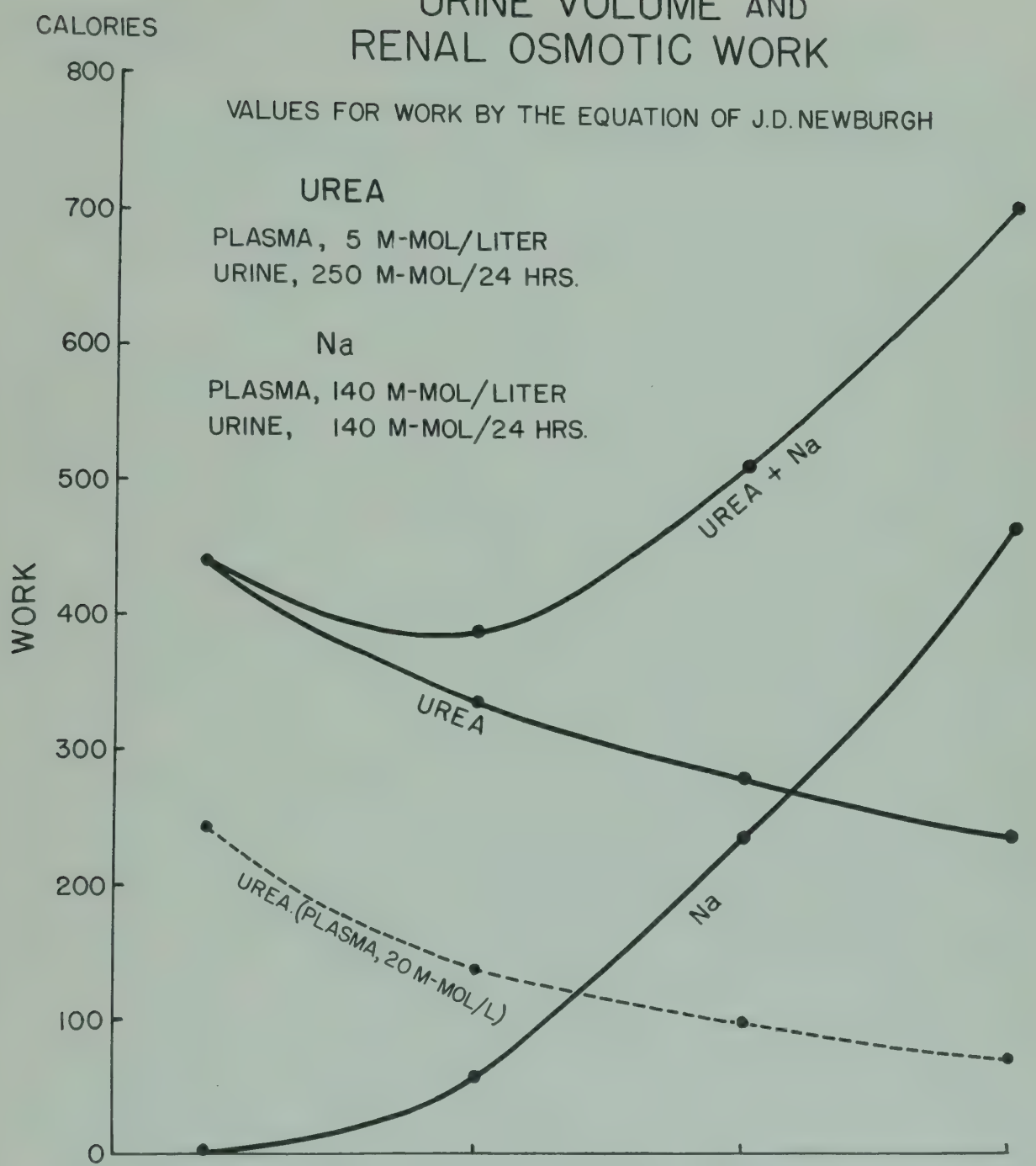
Obvious therapeutic indications are reduction of the urea load and a liberal water and salt intake. Reduction of the Na + Cl load by providing a salt-poor diet will greatly increase the work requirement for removal of Na and Cl and, in the presence of limited work capacity, the hazard of deficits.

The extensive reduction of filtration capacity found in advanced renal disease incidentally lowers the osmotic work requirement for removal of urea by raising plasma concentration (Chart 17-C) and thus provides, to variable extent, fortuitous compensation for reduction of work capacity, with corresponding limitation of polyuria. This is illustrated in the chart by the broken line curve which records the work requirement in relation to volume for removal of the urea load (250 milliosmols) when plasma concentration is raised to 20 millimols per liter; four times its usual value. As shown by the data, the resulting reduction of the work requirement for concentration of urea in urine permits removal of the load in 1 liter of urine at a limit of work capacity which would require 4 liters in the absence of elevation of plasma urea (upper urea curve).

It is physiologically interesting that, as shown in the chart, removal together of a usual load of urea + Na is accomplished with least work at the usual volume of urine.

It should be noted that estimation of osmotic work by the kidney at present requires the premise of equality of the work requirement for the individual components of urine in terms of their plasma-urine concentration differences. Several items of evidence indicate that, as might be expected for so intricate a process as selective reabsorption, this premise must be regarded as an approximation.

URINE VOLUME AND RENAL OSMOTIC WORK



UREA M-MOL/L	250	125	83	62.5
Na M-MOL/L	140	70	35	17.5

CHART 17-F

The history of the filtration-reabsorption method of renal control as related by E. K. Marshall and Homer Smith is an interesting tale of adventure of an evolutionary process. The glomerulo-tubule kidney first appears in the vertebrate fishes. According to recent interpretation of paleological evidence, the vertebrate fishes derive from fresh water ancestors and only in relatively recent geological times have fishes lived in the sea. The essential requirement for defense of extracellular fluid in a fresh water environment is conservation of substances in the presence of a very large removal of water. This was excellently met by the device of filtration followed by reabsorption from a large surface provided by a long tube. This kidney was not equipped to secrete urine hypertonic to blood plasma, an accomplishment for which there is no need in an hypotonic environment (water intake > salt intake, with respect to extracellular fluid tonicity). When fishes undertook to live in the sea they encountered the reverse challenge to osmotic independence; a greatly hypertonic environment (salt intake > water intake). Plasma filtration was evidently a disadvantage and the glomerulus was permitted to atrophy, so that most present day salt water fishes are partially or completely aglomerular. The kidney being unable to secrete urine above the osmotic level of plasma, an extrarenal device for the removal of electrolytes in excess of water was necessary. This is described in the next chart. The marine elasmobranch (cartilaginous) fishes have developed an ingenious additional defense of the electrolyte level which consists in adding on top of it the physiologically inert substance, urea, to an extent which brings the total osmotic value of plasma to approximately that of sea water. This permits the secretion of a much more concentrated, although still slightly hypotonic, urine. Incidentally this use of an unselectively diffusible substance clearly indicates that osmotic pressure per se is not physiologically significant. Osmotic mechanisms in the body fluids rest on the concentration level of the obligatorily extracellular electrolytes (Chart 14). It is also evident from these enormous concentrations of urea, that uremia is not by itself a poisonous predicament.

In man, and in most other terrestrial animals, an economical use of water is imperative. Coinciding with the addition of the loop of Henle, the glomerulo-tubule apparatus became able to secrete urine greatly hypertonic to plasma and thus meet water:salt removal requirements which are the reverse of those for which it was originally designed. As may be seen in the chart the plasma electrolyte concentration in man is almost exactly the same as is found in the fresh water teleost (bony) fishes. As a result, however, of

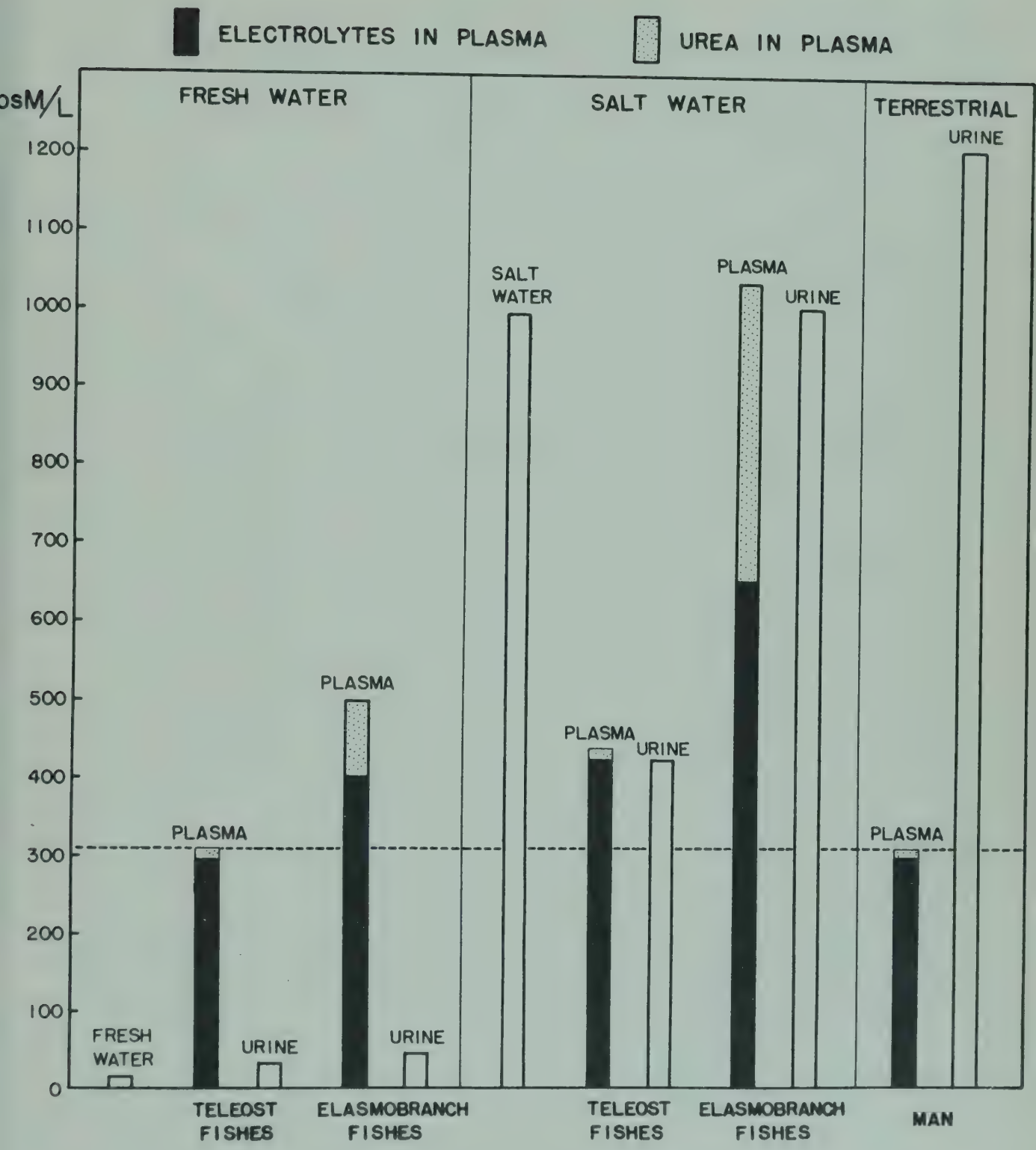

ELECTROLYTES IN PLASMA
UREA IN PLASMA
osM/L
FRESH WATER
SALT WATER
TERRESTRIAL
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
FRESH WATER
PLASMA
URINE
PLASMA
URINE
SALT WATER
PLASMA
URINE
PLASMA
URINE
PLASMA
URINE
TELEOST FISHES
ELASMOBRANCH FISHES
TELEOST FISHES
ELASMOBRANCH FISHES
MAN

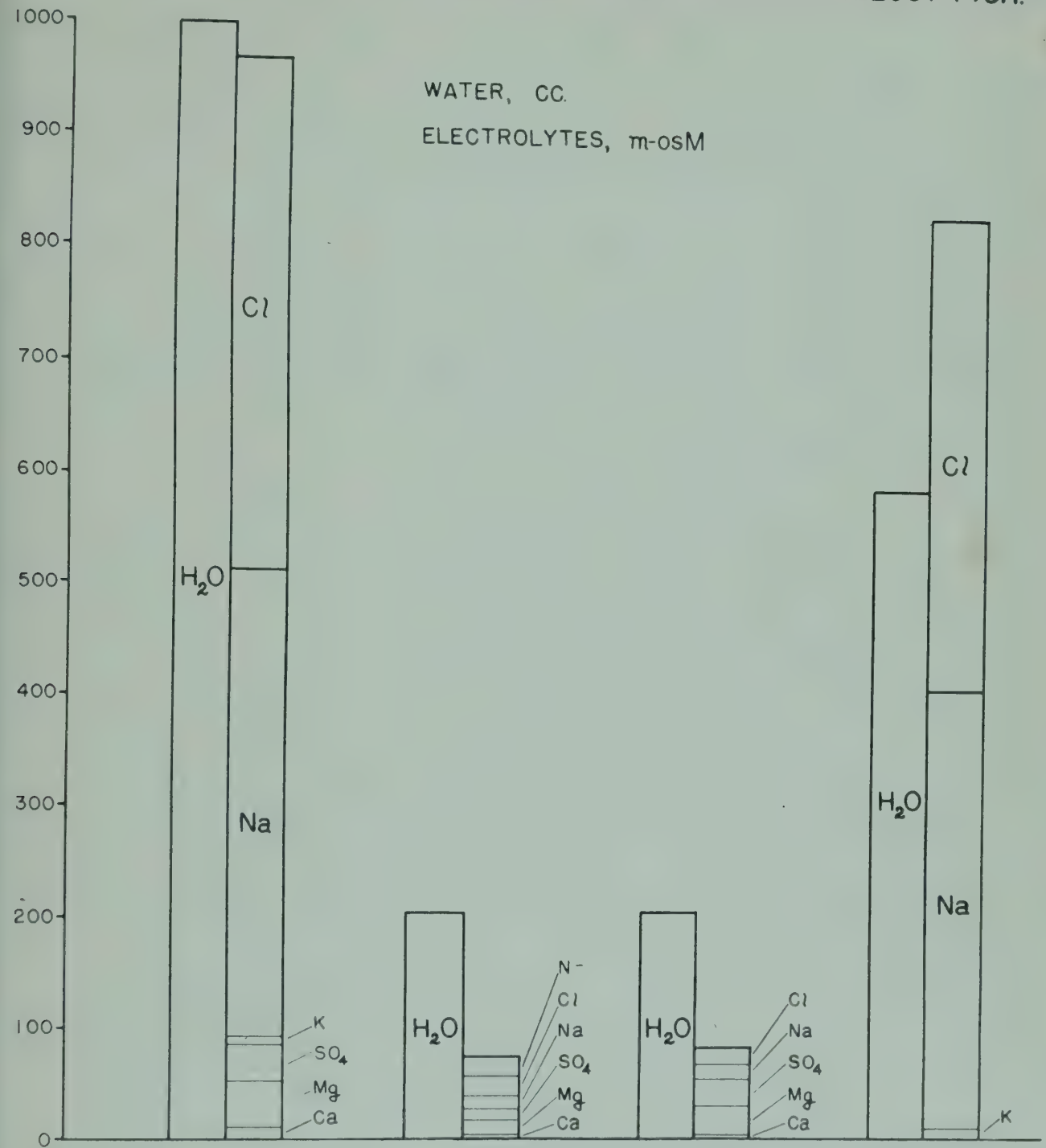
CHART 18

having inherited a "fresh water" kidney, about 180 liters of water and more than a kilogram of salt must be reabsorbed daily. Although this round-about method of control is, according to this account, fortuitous, it must be admitted that it works with a beautiful accuracy.

CHART 19

Osmoregulation in the marine fishes consists in defense of the biologically prescribed value for the concentration of electrolytes in body fluids against the three times superior osmotic pressure of present-day sea water. They have been provided with the obviously indicated impermeable cuticle. Sea water enters the fish only by ingestion. It has been shown that the gastro-intestinal tract is unable to selectively absorb water. The requirement is, therefore, produced for the removal of salts of absorbed sea water with an expenditure of water no greater than sea water provides. This the kidney, devised to suit an hypotonic environment, is unable to do. It cannot excrete urine of an osmotic pressure above that of the plasma, which is only one-third that of sea water and is therefore obliged to spend three parts of the water from ingested sea water on the removal of one part of salt. In other words, the kidney not only is incapable of defending the osmotic value of the plasma, but actually operates in the reverse direction. The salt concentration of intestinal residue is lowered to that of the body fluids. So there is here the same loss of water with respect to salt as in the urine. These two items of water wastage produce the requirement for removal of the remainder of the ingested salt at a concentration above that of sea water. Homer Smith has most interestingly shown that this feat is accomplished by the gills. His data, obtained from a fasting eel, have been used to construct the diagrams in this chart which give an approximately complete account of the water and electrolyte exchange of a marine teleost. The diagrams define the water expenditures in excess of electrolyte in urine and intestinal residue and the compensatory economy of water in the removal of electrolyte by the gills. The concentration values which the data in the diagrams produce are recorded at the foot of the chart. From them it may be seen that the bulk of the electrolyte intake is removed by the gills at a concentration which is nearly one and one-half times that of the surrounding medium and four times the osmotic value of the internal medium (accepting the urine value as approximately that of blood plasma). Interestingly this fourfold osmotic gradient sustained by the gills also approximately defines the concentrating capacity of the mammalian kidney equipped with the loop of Henle (preceding chart).

EXCRETION OF 1 LITRE OF INGESTED SEA WATER BY A TELEOST FISH.



SEA WATER	URINE	INTESTINAL RESIDUE	EXCRETION BY GILLS
0.97 M/L	0.36 M/L	0.40 M/L	1.41 M/L

CHART 19

Although the mechanisms of selective reabsorption are still invisible, they require certain acid-base adjustments in the construction of urine which can be examined. Because of irregularity in the composition of the food intake, variably unequal quantities of base and acid are presented for removal in urine. The permissible range of reaction, from pH 7.8 to pH 4.8, is much wider on the acid side than in plasma. But even a usual food intake requires excretion of an excess of acid over base which, if uncontrolled, would produce a pH far beyond the limit of urine acidity. Occasionally when alkaline articles of food are predominant, base must be removed in excess of acid. There is therefore obvious need for defensive adjustments which will permit the process of selective reabsorption to operate within the boundaries which have been set for the reaction of urine.

The mechanism which manages the removal from plasma of acid in excess of base is composed of two interoperating parts; a direct saving of base gained by secretion of urine of an acidity within the prescribed limit and a regulated substitution of ammonium for plasma base (fixed base) in covering acid radicals as they enter the urine. Saving of base by secretion of acid urine can be accomplished only in the removal of the two weakly acid components of the acid excretion; phosphate ion and the several organic acids, which, since they can be measured together by the titration method of Palmer and Van Slyke, are conveniently dealt with as a unit. As may be seen in Chart 20, HPO''_4 is conveyed in plasma (pH 7.4) almost entirely as dibasic phosphate, but can be removed in urine at the limit of acidity (pH 4.8) as monobasic phosphate. Its excretion may therefore be accomplished with an expenditure of only slightly more than one-half of the base which covers it in plasma. Similarly, in the case of citric acid, a prominent component of the group of organic acids, a considerable portion can be removed in acid urine base free, whereas in plasma it must be completely covered by base. The other two components of the acid excretion, Cl' and SO''_4 being radicals of strong acids must carry their full equivalence of base into the urine.

A quantitative view of these two adjustments which defend plasma base is provided by the measurements given below which were obtained from a twenty-four hour urine collection from a healthy adult on an ordinary diet. The values used for the base equivalence of HPO''_4 and of the organic acids, according to the pH of urine,

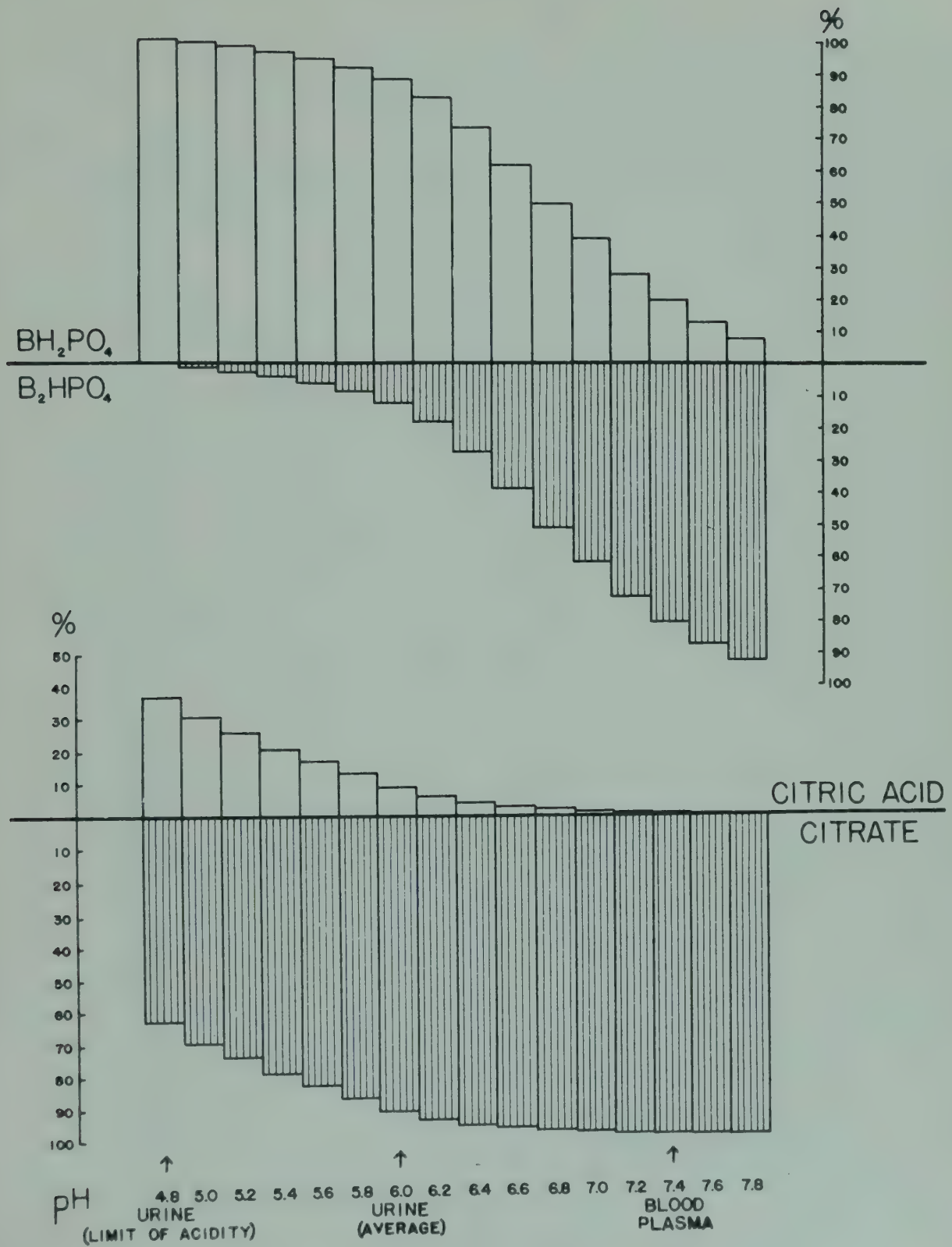

%
100
90
80
70
60
50
40
30
20
10
BH_2PO_4
B_2HPO_4
10
20
30
40
50
60
70
80
90
100
%
50
40
30
20
10
CITRIC ACID
CITRATE
10
20
30
40
50
60
70
80
90
100
pH
4.8 5.0 5.2 5.4 5.6 5.8 6.0 6.2 6.4 6.6 6.8 7.0 7.2 7.4 7.6 7.8
URINE
(LIMIT OF ACIDITY)
URINE
(AVERAGE)
BLOOD
PLASMA

CHART 20

derive from the ratios shown in Chart 20. For example at the pH of blood plasma the proportion of BH_2PO_4 to B_2HPO_4 is 0.2:0.8. The base equivalence of HPO_4'' is therefore 0.2 + (2 x 0.8) = 1.8. In urine of the reaction of the specimen, pH 5.4, the proportion is 0.96:0.04 and base equivalence is 0.96 + (2 x 0.04) = 1.04.

A. Acid excretion in terms of base equivalence at pH 7.4 (plasma)

Cl'	119 m-M x 1.0 =	119 m-Eq.
SO_4''	23 m-M x 2.0 =	46 m-Eq.
HPO_4''	30 m-M x 1.8 =	54 m-Eq.
*Organ. Ac.	37 meq. x 1.0 =	37 m-Eq.
		256

B. Fixed Base excretion

$Na^{\cdot}$	108 m-M x 1.0 =	108 m-Eq.
$K^{\cdot}$	60 m-M x 1.0 =	60 m-Eq.
$Ca^{\cdot\cdot}$	2.5 m-M x 2.0 =	5 m-Eq.
$Mg^{\cdot\cdot}$	4 m-M x 2.0 =	8 m-Eq.
		181

A′. Acid excretion in terms of base equivalence at pH 5.4 (urine)

Cl'	119 m-M x 1.0 =	119 m-Eq.
SO_4''	23 m-M x 2.0 =	46 m-Eq.
HPO_4''	30 m-M x 1.04 =	31 m-Eq.
Organ. Ac.	37 meq. x 0.8 =	30 m-Eq.
		226

B. Ammonium production

$NH_4^{\cdot}$	44 m-M x 1.0 =	44 m-Eq.
Acid excess at plasma pH, A-B	=	75 m-Eq.
Base economy by acid urine, A-A′	=	30 m-Eq.
Remainder of acid excess		45
Ammonium, directly measured		44 m-Eq.

*(The titration method of determination defines complete equivalence but does not measure molecular concentration.)

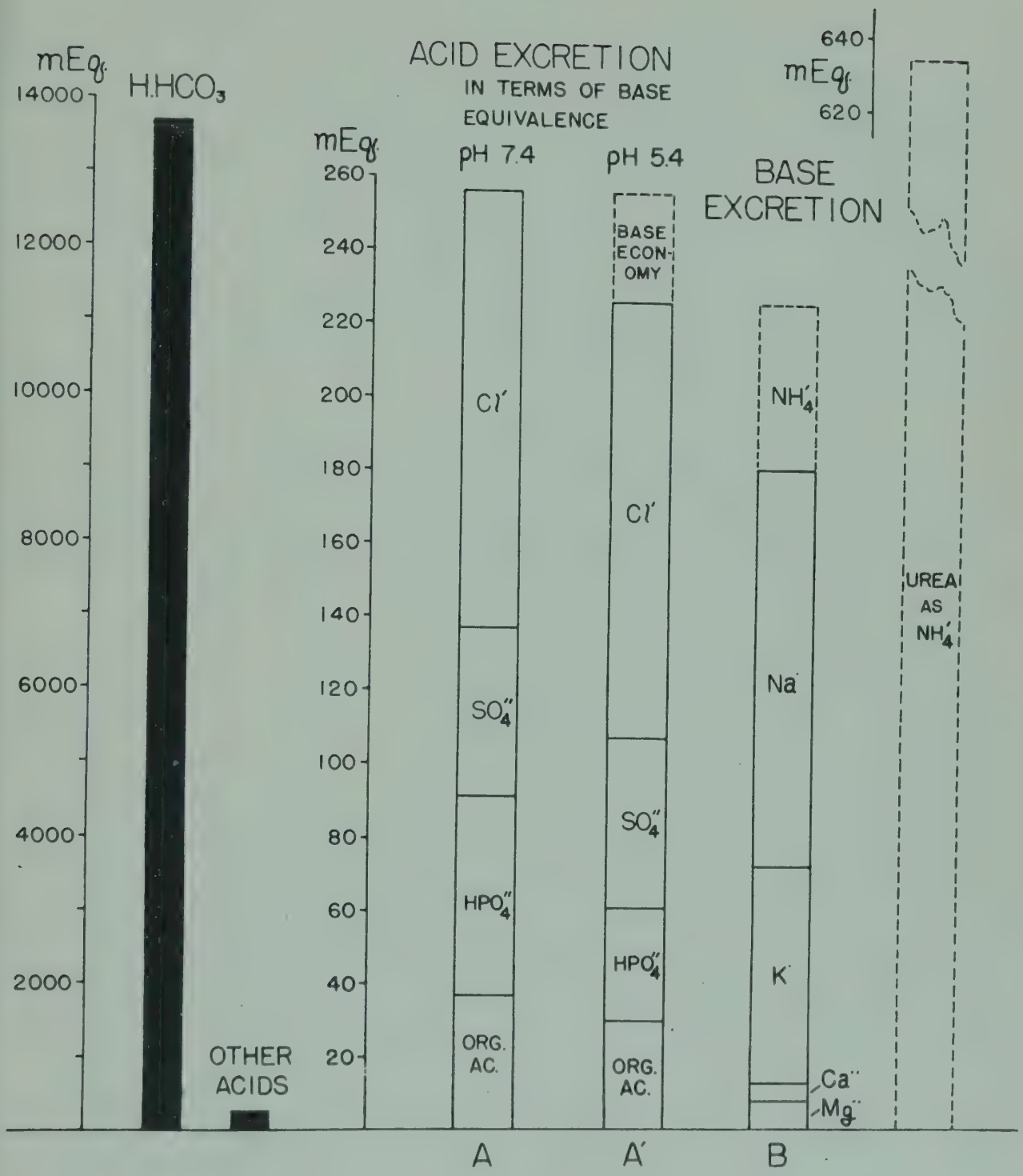

mEq.
14000
12000
10000
8000
6000
4000
2000
H.HCO3
OTHER ACIDS
ACID EXCRETION
IN TERMS OF BASE EQUIVALENCE
mEq.
260
240
220
200
180
160
140
120
100
80
60
40
20
pH 7.4
pH 5.4
Cl'
SO4''
HPO4''
ORG. AC.
BASE ECON-OMY
Cl'
SO4''
HPO4''
ORG. AC.
A
A'
BASE EXCRETION
640
mEq.
620
NH4'
Na'
K'
Ca''
Mg''
B
UREA AS NH4'

CHART 21

This illustrative analysis of the process of removal from blood plasma of acid in excess of fixed base is graphically described in Chart 21 Ammonium production is seen to be the larger of the two control adjustments. The practically unlimited availability of ammonium is shown by the last column in the chart which measures the urea excretion in terms of potential ammonium. Although the capacity of the base economy factor of control is relatively small, it has an immediate and very accurate adjustability. The larger ammonium factor moves much more slowly and, in consequence, with less precision. These two parts of the mechanism which conserves plasma base may be compared to the fine and the coarse adjustments of a microscope.

The relatively enormous value (about 2 pounds daily) of the largest end product of metabolism, carbonic acid, is shown in the chart. Routinely this acid is removed, without an expenditure of base, by the lungs. Under certain circumstances, however, an adjusted quantity of carbonic acid carries base into the urine (Chart 24).

CHART 22

The data on this chart will serve to illustrate the operation together of the two factors of regulation, base economy and ammonium production, which control the use of fixed base in the process of acid excretion. The measurements used in constructing the diagrams are from consecutive 24-hour collections of urine over a 4-day period of fasting and a 2-day after period during which a small amount of carbohydrate was given in the form of cane sugar. The subject was an epileptic child who was fasted as a therapeutic measure. During fasting HPO_4'' and SO_4'' presenting for excretion derive from consumption of body protoplasm and Cl' from reduction of volume of extracellular fluid, and from these sources there is released for removal in urine a roughly equivalent quantity of base. A large excess of acid over base excretion develops, however, from extension of the excretion of organic acids due to addition of incompletely oxidized fatty acids. This ketosis is promptly removed by supplying glucose, which also, by its protein sparing effect, causes a large reduction in the quantities of the other acid radi-

SHOWING CONSERVATION OF FIXED BASE
IN THE PROCESS OF ACID EXCRETION

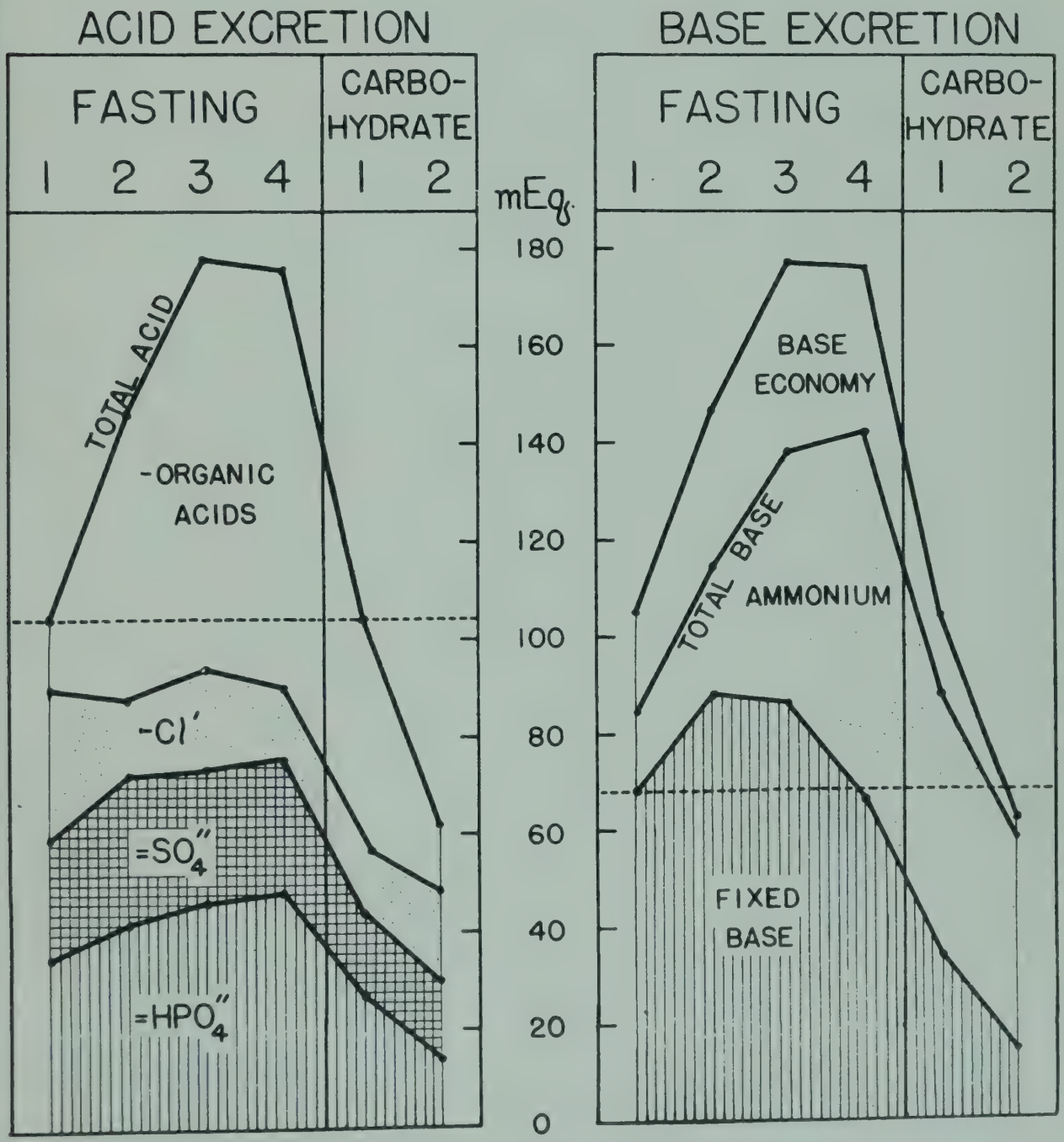


CHART 22

cals, and of fixed base presenting for excretion. There is, thus, over the two periods of this experiment, large and rapid change in the factors of acid-base excretion, requiring alert and extensive adjustment of the factors of regulation which defend the fixed base content of extracellular fluid.

The measurements obtained from the specimens were of the four factors of the acid excretion, of ammonium, and of base economy. The value for base economy can, as was pointed out by Lawrence Henderson, be easily obtained by titrating the urine with standard alkali to pH 7.4, the reaction of blood plasma. The extent of plasma base conservation gained by secretion of acid urine is thus measured. In this study the four components of the fixed base excretion were not directly measured. The values for fixed base, recorded in the chart, were obtained by subtracting the sum of the measurements of base economy and ammonium from the sum of the values found for the four components of acid excretion in terms of their base equivalence at the reaction of blood plasma. Reference to Chart 21 will make this computation clear. The two factors controlling the use of fixed base in the process of acid excretion are thus given quantitative description and it is seen that a total acid excretion which, while being conveyed to the kidney, was completely covered by fixed base, is managed with an expenditure of fixed base amounting to about one-half ot its plasma equivalence. The diagram shows very clearly the wide adjustability of this control.

CHART 23

In the preceding chart the process of removing an acid excess in urine is described in terms of control of the total fixed base excretion. Obviously, this is an incomplete account of a mechanism which must defend the several components of extracellular fluid base individually. In the situation produced by fasting there is continuous release of K and Mg by consumption of protoplasm and an absorption of Ca from deposits, presumably caused by the acidosis of fasting. The relatively small concentrations of these ions in extracellular fluid thus have the support of an abundant intake. Sodium which composes 92% of the total base value, because of its exclusively extracellular position, has no source of support.

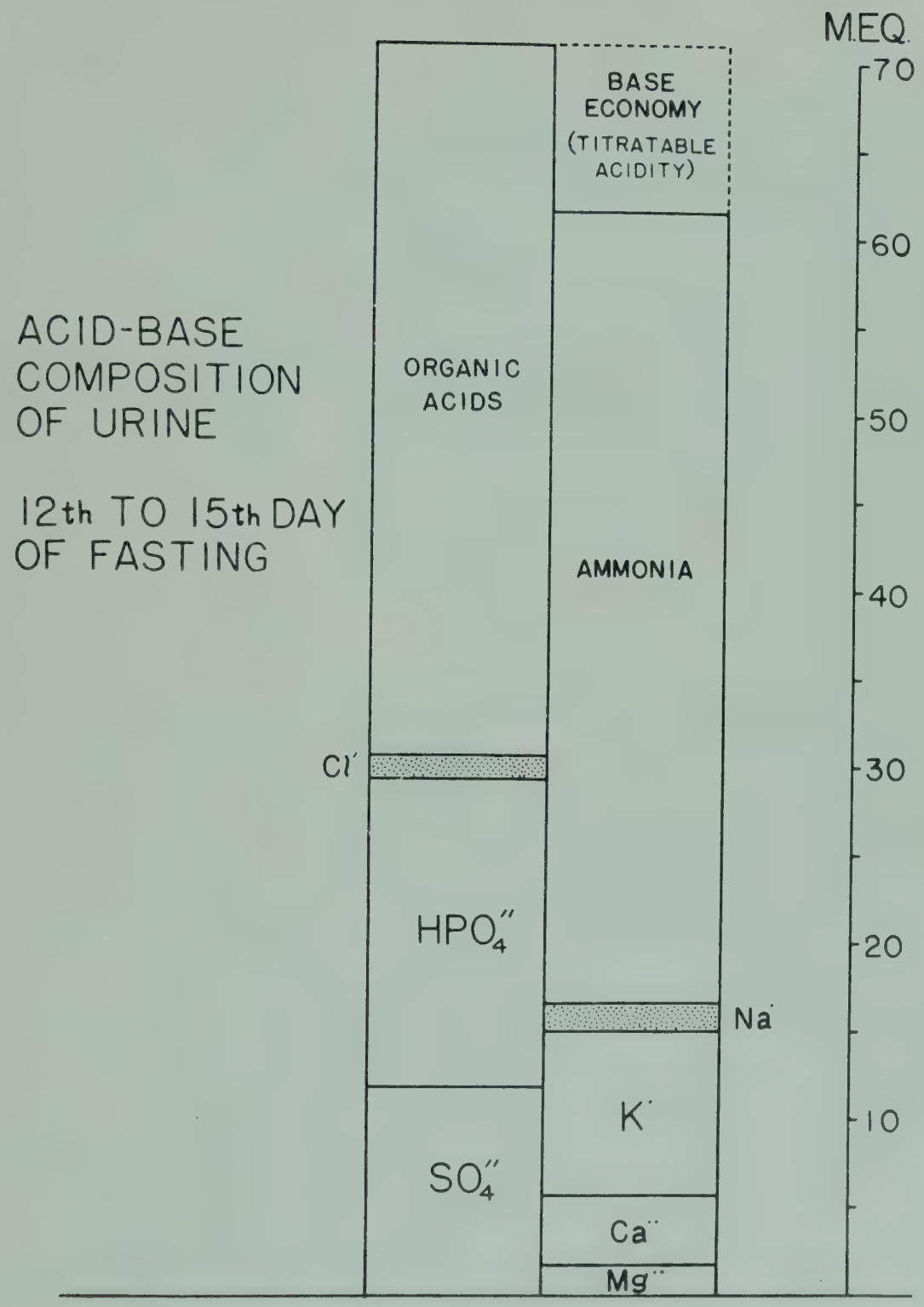

ACID-BASE
COMPOSITION
OF URINE
12th TO 15th DAY
OF FASTING
MEQ.
70
60
50
40
30
20
10
BASE
ECONOMY
(TITRATABLE
ACIDITY)
ORGANIC
ACIDS
AMMONIA
Cl'
HPO4''
Na'
K'
SO4''
Ca''
Mg''

CHART 23

Conservation of sodium is therefore the outstanding requirement in the regulation of fixed base excretion during fasting.

This chart describes the acid-base composition of urine during the later part of a prolonged fast. Sodium is found to be a small factor in the fixed base excretion. On the acid side of the diagram may be noted a corresponding restraint of the excretion of the other large factor of extracellular fluid structure, chloride ion. It is probable that the presence in the urine of these small quantities of sodium and chloride ion represent an appropriate reduction of extracellular fluid volume along with the decrease of total protoplasmic mass caused by fasting, rather than imperfect conservation.

CHART 24

Not infrequently, instead of the usual excess of acid over fixed base claiming excretion in urine, the quantity of fixed base to be removed is larger than the sum of the acid radicals. There is here need for an acid analogue of ammonium; that is, an acid substance which is abundantly at hand and can be controllably placed in the urine. Carbonic acid suits these specifications ideally. Its availability is practically unlimited (Chart 21). Routinely it leaves the body base free by way of the lungs, but when needed can, to a regulated extent, be deflected into the urine.

Measurements of the concentrations of carbonic acid and of bicarbonate in urine reveal the interesting relationship shown in this chart. Carbonic acid is found to have a nearly stationary concentration of approximately the value sustained in blood plasma. Carbonic acid is unique in this respect; all of the other components of urine being found at widely varying concentrations, usually above their plasma levels (Chart 15). Evidently the concentration of carbonic acid in urine rests, as does its plasma value, on the carbon dioxide tension in the residual air of the lungs, and is not controlled by the kidney but simply diffuses into the urine. Since hydrogen ion concentration is determined by the ratio of the concentrations of free carbonic acid and bicarbonate, this fixed value for the numerator of the ratio prescribes the individual values for bicarbonate over the range of urine reaction. These are recorded

CARBONIC ACID AND BICARBONATE IN URINE

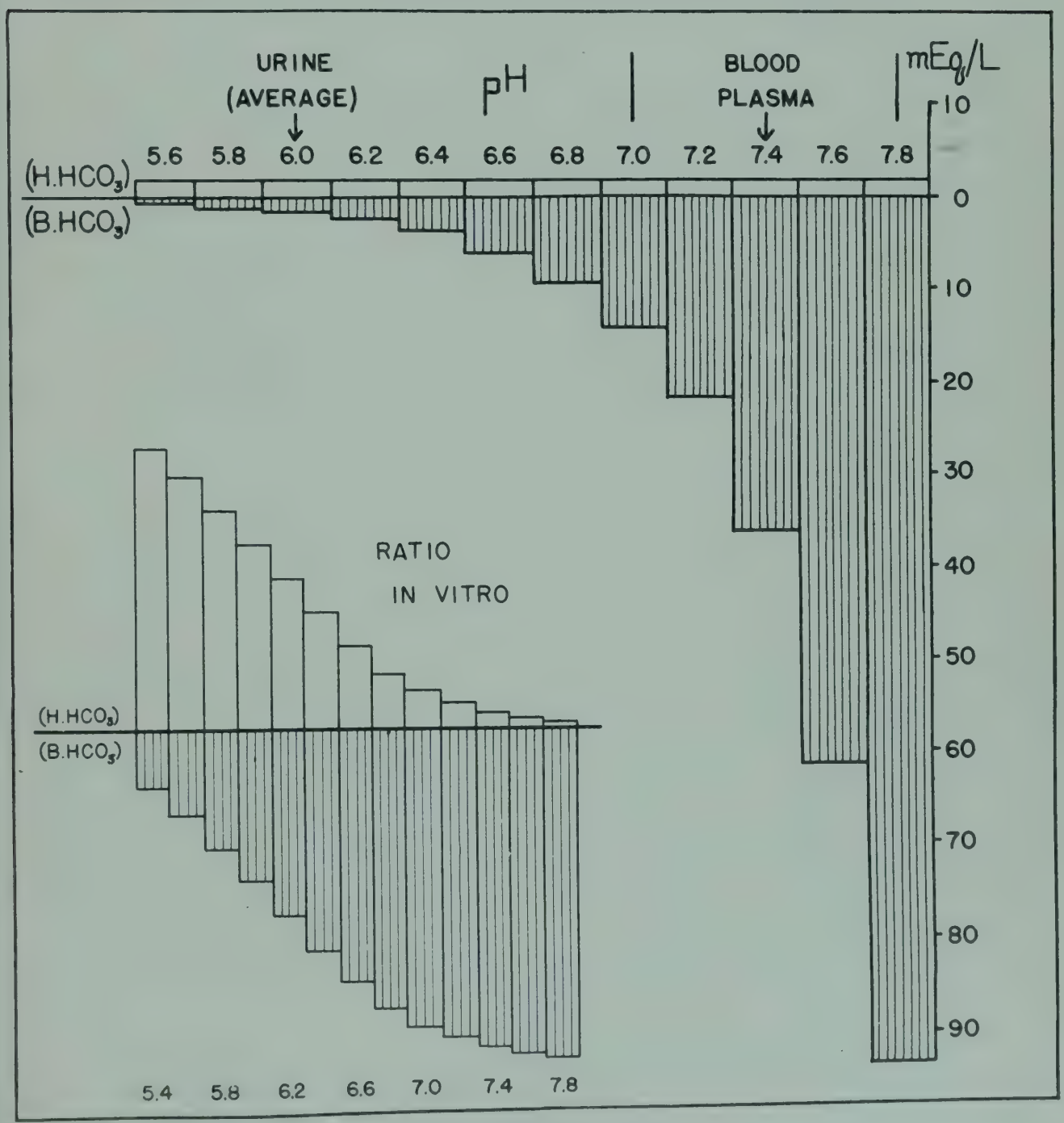


CHART 24

in the chart and it will be seen that, as reaction moves in the direction of alkalinity, the bicarbonate values rapidly become very large. The fixed numerator for the $(H.HCO_3):(B.HCO_3)$ ratio thus provides a simple and excellent mechanism for the removal in urine of fixed base in excess of acid within the alkaline boundary of urine reaction. The extra base is removed as bicarbonate and, beyond the reaction of blood plasma, progressively enormous quantities of base as bicarbonate can be placed in urine within a very small range of reaction change. An alkaline boundary which is only a small distance from plasma reaction is thus easily defended.

Proper admiration for the device of a fixed value for carbonic acid may be gained by inspecting the smaller diagram which describes ordinary unguided bicarbonate buffering. Here changes in the denominator of the ratio produce reciprocal change in the numerator with the result that the steps in bicarbonate change, with respect to pH, are very much smaller than those found in the urine. The functional superiority of the urine ratio in providing a wide range of control of base entering the urine as bicarbonate is clearly evident. This is especially conspicuous on the alkaline side of pH 7.4 where the uncontrolled ratio permits very small increments of bicarbonate to move pH to 7.8, and therefore would offer almost no defense of the alkaline boundary of urine which the urine ratio guards with an almost ideal effectiveness. The stationary value for $(H.HCO_3)$ rests, as has been mentioned, on the rapid diffusibility of carbonic acid. Depletion of $(H.HCO_3)$ by extension of $(B.HCO_3)$ is immediately replenished and increase by release from $(B.HCO_3)$ is quickly removed. Diffusion from bladder urine is probably slow. Addition of urine of low pH to urine of high pH should release carbonic acid. This is the probable explanation of occasional large deviations from the usual value which have been reported.

CHART 25

The removal of fixed base as bicarbonate in defense of the anion components of the plasma, particularly chloride ion, is illustrated by measurements obtained from an animal experiment and recorded in this chart. The circumstances of acid-base excretion which they describe obtain clinically when dehydration (reduction of extracellular fluid volume) caused by vomiting is treated by ad-

ILLUSTRATING EXCRETION OF HCO_3' IN URINE
IN DEFENCE OF (Cl') IN BODY FLUIDS

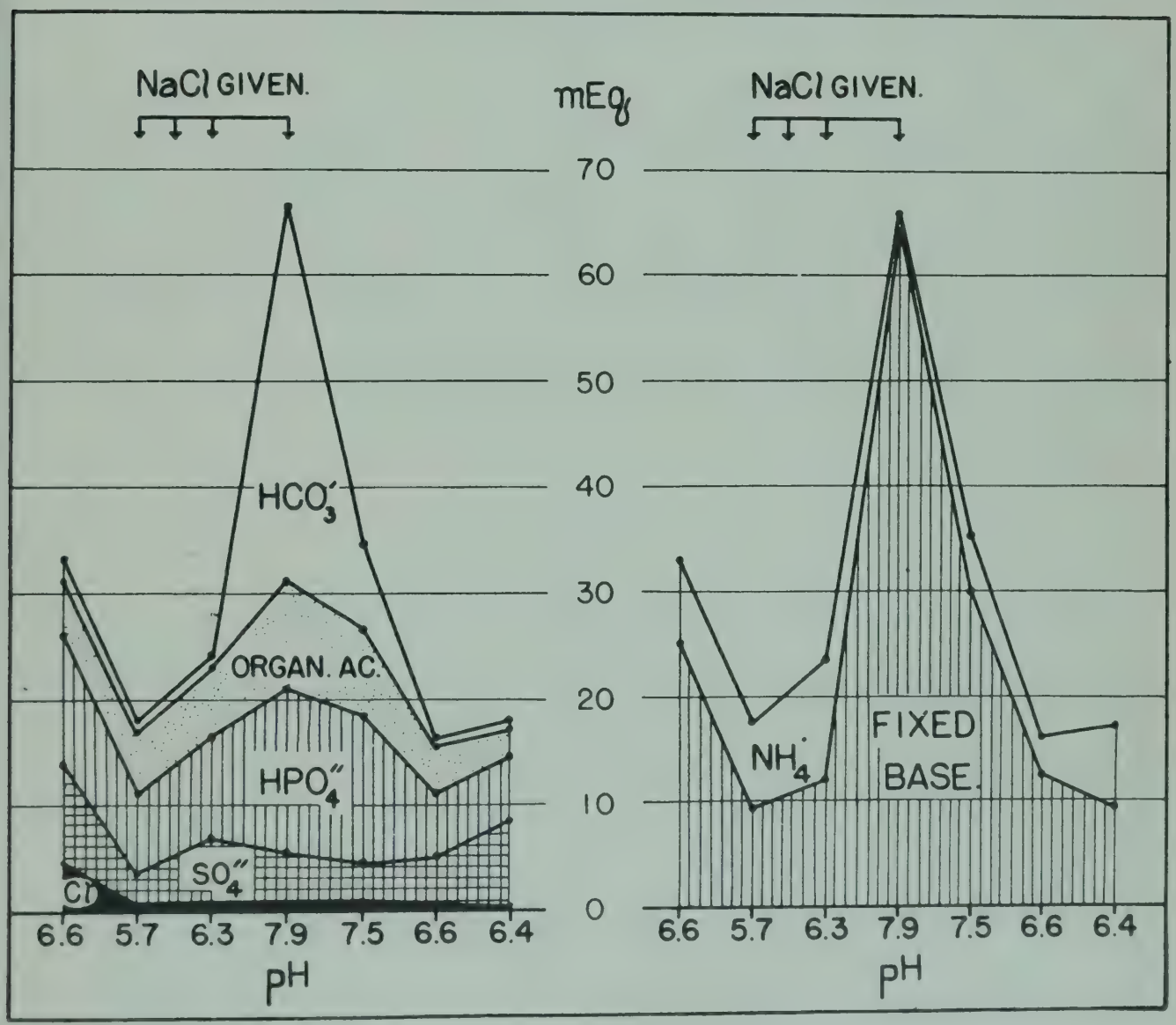


CHART 25

ministration of salt solution. The experiment consisted in obstructing the pylorus of a female dog by ligature. Then, after permitting dehydration caused by loss of stomach secretions to proceed for two days, large quantities of salt solution were given by intraperitoneal injection. Owing to the larger loss of chloride ion than of sodium in stomach secretions, the sodium deficit is replaced from the administered salt solution long before that for chloride ion. The kidney is then called upon to remove sodium but to continue to retain chloride ion. Measurements of the individual acid radicals, ammonium and fixed base were obtained from consecutive 12-hour catheter collections of urine. The values found for the acid radicals are superimposed in the left-hand diagram. The excretion of chloride ion is seen to remain at a small value throughout the experiment, indicating that the quantity of salt solution given was not enough to entirely replace the loss of chloride ion. In the other diagram, following the third injection of salt solution, an extensive rise in fixed base excretion is found. This represents removal of surplus sodium. In the diagram of the acid excretion it is seen to be covered by a peak in total acid composed of bicarbonate ion.

CHART 26

The diagrams in this chart are constructed from the measurements obtained from the urine collected over the fourth 12-hour period of the experiment described by the preceding chart. This specimen contained most of the sodium surplus and its pH value was 7.9. The diagrams describe quantitatively the saving of chloride gained by the secretion of urine at pH 7.9 instead of at the usual reaction of urine, pH 6.0. Acid-base composition as directly determined is described by the first diagram. The measurements of the organic acid and phosphate ion excretions are recorded in terms of their base equivalence at pH 7.9 (Chart 20). The second diagram is constructed from the found values for the excretion of base, organic acids, phosphate ion, and sulfate ion. The minute value for bicarbonate ion is derived from the concentration found in urine at pH 6.0 (defined in Chart 24). It will also be noted that the base equivalence of the organic acids and of phosphate ion is considerably less than at pH 7.9. There is thus left a large remainder, more than half, of the acid column in the diagram, which would have

ILLUSTRATING CONSERVATION OF (Cl') IN BODY FLUIDS BY EXCRETION OF HCO_3' IN URINE.

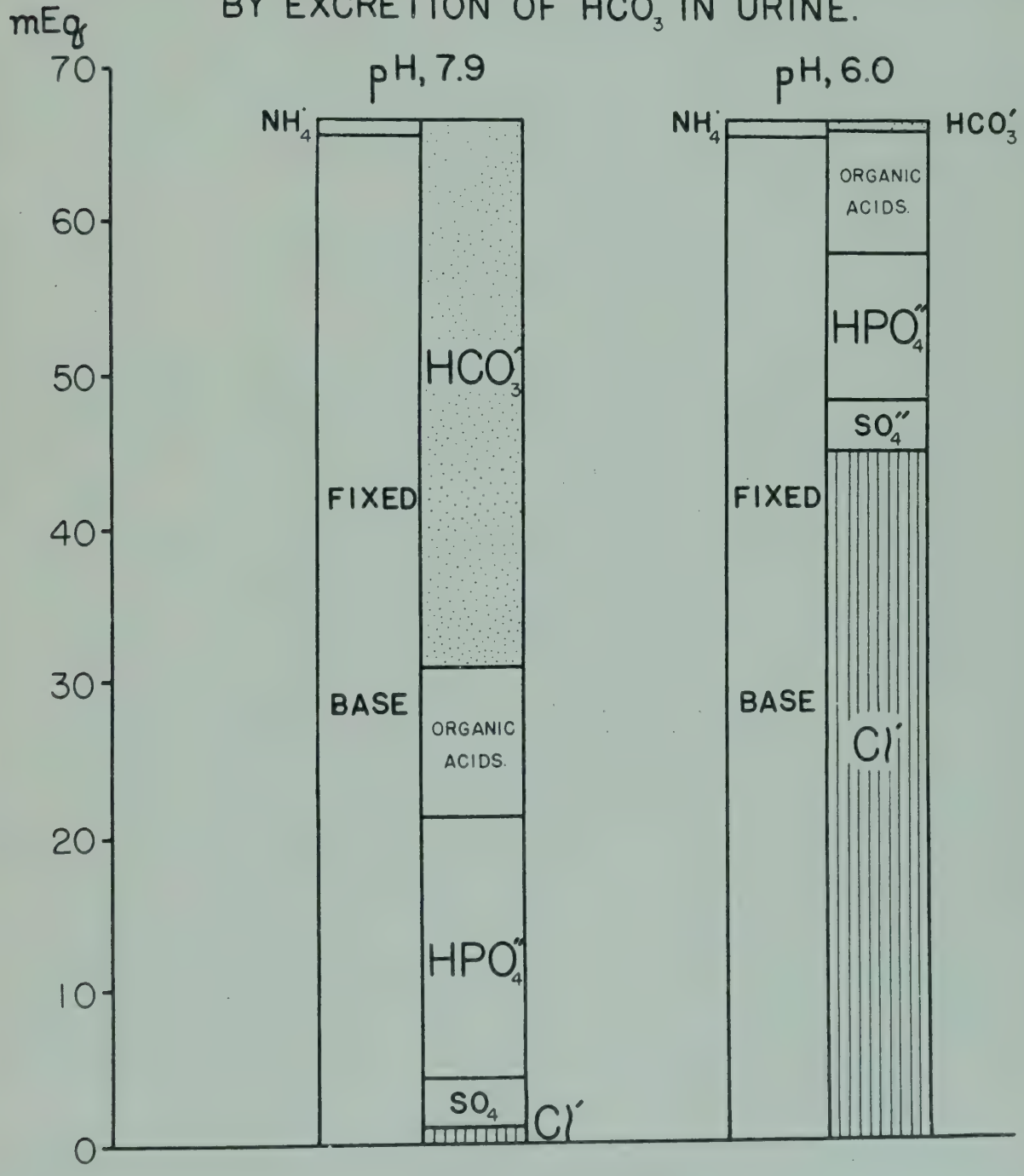


CHART 26

to be filled with chloride ion from the administered salt solution.

By way of emphasizing that the word salt has no biological meaning, it may be noted that the kidney, dealing with plasma ions in terms of their individual requirements, secretes in the above described situation an intensely alkaline urine following the administration of a neutral salt.

CHART 27

Returning to Chart 24, a point may be noted which relates, not to removal of an excess of fixed base, but to base conservation. In urine of the reaction of blood plasma, the chart records a quantity of bicarbonate which is very large as compared with the bicarbonate content of the urine at the average reaction of urine, pH 6.0. Since carbonic acid can be removed from the body base free by way of the lungs, base as bicarbonate in the urine, under circumstances demanding conservation of base, must be regarded as base wasted. Avoidance of useless expenditure of base as bicarbonate can therefore be recognized as a chief significance of the usual reaction of urine. Obviously, there is here a saving of base separate from, and additional to, the economy of base gained by the removal of organic acids and the radical of phosphoric acid in urine of lower pH than blood plasma (A - A' Chart 21). The diagrams on the opposite page provide a quantitative view of these two items of base conservation. The first diagram describes the acid-base composition found in a specimen of urine secreted at pH 5.2. The other diagram defines the much larger quantity of base which would have to be present if the same quantities of the acid radicals were removed in urine of the reaction of blood plasma. This increment is composed of extension of the base equivalence of the organic acids and phosphate ion and the presence of an even larger quantity of base as bicarbonate.

The balance sheet of acid-base excretion given in Chart 21 defines a minimal expenditure of base required by the four acid radicals which must be removed in urine. Carbonic acid therefore does not enter into this accounting and the item of base conservation which consists in the absence of bicarbonate from very acid urine does not appear.

SHOWING FACTORS OF REDUCTION
OF BASE EXCRETION IN ACID URINE.

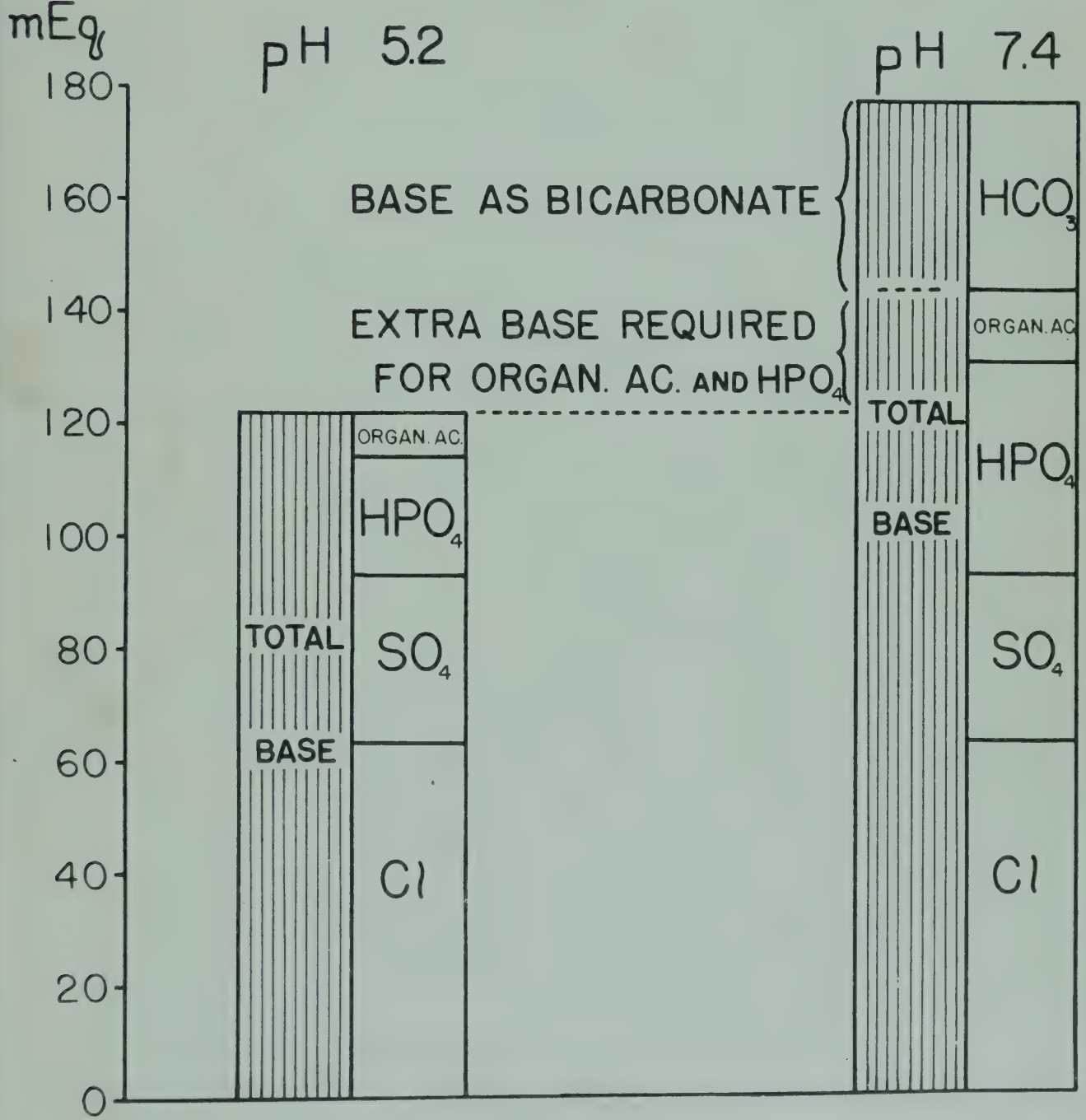


CHART 27

The two items of base conservation shown in the preceding chart make clear the great advantage of the permissible range of pH in urine. The movement of pH, as Van Slyke and coworkers have pointed out, can be explained very simply and probably correctly as a consequence of the process of selective reabsorption of the components of glomerular filtrate. This chart is intended to illustrate in quantitative terms the (A):(BA) changes in the three sets of buffering substances in urine caused by adjustment of base return to the plasma. The (A) and (BA) values are computed for 1.5 liters of urine containing 30 millimols of phosphate ion and 40 milliequivalents of organic acids. These are roughly average 24-hour quantities. The concentrations of carbonic acid and bicarbonate are those given in Chart 24. The individual values for the components of total (A) and (BA) are superimposed. The relative quantities of the buffering substances in urine at the reaction of glomerular filtrate are shown in the column at pH 7.4. The columns on the alkaline side of pH 7.4 describe the changes caused by reabsorption of anion in excess of fixed base. On the acid side this process is reversed by reabsorption of base from BA with consequent release in the urine of A. The values for (BA) over the range of urine pH will be easily understood if it be recalled that in the case of the phosphate ion and organic acid excretions, the steps in the removal of B from BA produce corresponding increments of A (Chart 20), whereas removal of base from bicarbonate does not alter the concentration of carbonic acid in urine. The stationary numerator for the $(H.HCO_3):(B.HCO_3)$ ratio, which rests on the rapid diffusibility of carbonic acid, produces the wide range of values for $(B.HCO_3)$ seen in Chart 24 and thus enables bicarbonate to contribute much more extensively to base adjustments than the BA fractions of the other two buffering substances. The effectiveness of this device is especially evident on the alkaline side of pH 7.4. Here the reabsorption of anion in excess of fixed base is accomplished almost entirely, and with only a small movement of pH, by the large extensions of bicarbonate produced by the persistent presence of free carbonic acid. At the outset of the reverse process, base conservation by reabsorption of B from BA with release of A, bicarbonate is again the prominent factor and provides the greater part of the base until it approaches the point where it is completely removed from the urine. Thereafter, from the usual reaction of the urine, pH 6.0, onward in the direction of acidity base is obtained in much smaller steps from the BA fractions of the phosphate ion and organic acid excretions.

Owing to the stationary value for $(H.HCO_3)$, increase in

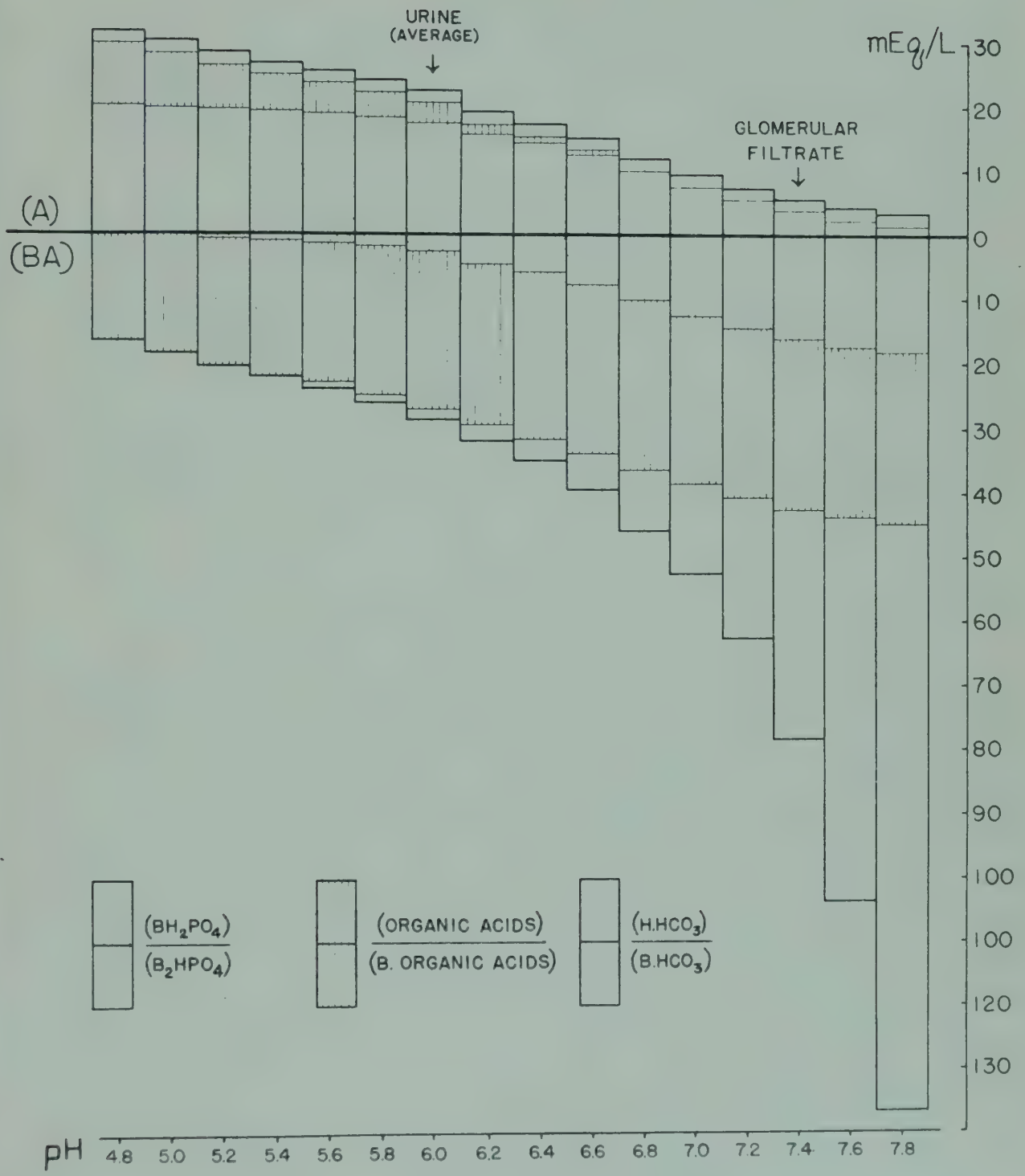

URINE
(AVERAGE)
GLOMERULAR
FILTRATE
mEq/L
(A)
(BA)
30
20
10
0
10
20
30
40
50
60
70
80
90
100
100
120
130
(BH2PO4)
(B2HPO4)
(ORGANIC ACIDS)
(B. ORGANIC ACIDS)
(H.HCO3)
(B.HCO3)
pH
4.8
5.0
5.2
5.4
5.6
5.8
6.0
6.2
6.4
6.6
6.8
7.0
7.2
7.4
7.6
7.8

CHART 28

urine acidity is composed of acid phosphate and (beyond pH 6.0) free organic acids. Although acid phosphate is the larger component, it may be noted that it is chiefly the increments of organic acid that carry the reaction of the urine beyond pH 6.0. Economy of base in the removal of phosphate ion and the organic acids, as has been considered (Charts 20 and 21), may be measured by titrating the urine with standard alkali to the reaction of blood plasma. The extent of this saving of base at the acid limit of urine as defined by the data in the chart, is 26 milliequivalents per liter (obtained by subtracting (A) at pH 7.4 from (A) at pH 4.8). Since the superimposed values for acid phosphate and organic acids define in the chart a roughly linear relationship between (A) and pH, and since the range of pH change is 26 tenths (7.4 - 4.8 = 2.6), it may be roughly stated that, according to these data from an "average" urine, each reduction of pH by 0.1 produces a saving of one milliequivalent of base in the removal of these two components of the acid excretion.

CHART 29

The quantity of fixed base which can be taken from the BA fractions of the phosphate ion and organic acid content of glomerular filtrate by the process of selective reabsorption within the acid boundary of urine (Chart 28), is usually less than half of the excess of acid over fixed base claiming excretion in the urine (Chart 21). The further reabsorption of fixed base, which is necessary to avoid plasma deficit, is provided for by the substitution in urine of ammonium for fixed base to the extent of the remainder of the acid excess. According to recent evidence, this regulated release of ammonium takes place in the kidney and the ammonium is obtained, not from urea, but from the amino acids of glomerular filtrate. The quantity of ammonium found in blood plasma is very minute and, moreover, is possibly an artifact of the technic of measurement. It is a premise of acid-base metabolism that the base ammonium cannot be used to an appreciable extent in body fluids but can be used for the covering of acid radicals in the urine. It is this circumstance which makes necessary the designation of plasma base as "fixed" base. As regards the interoperation of the two adjustments which control fixed base removal in urine, direct base saving (base economy) and the substitution of ammonium (Chart 21), it may be noted that they proceed together, and not en echelon, with

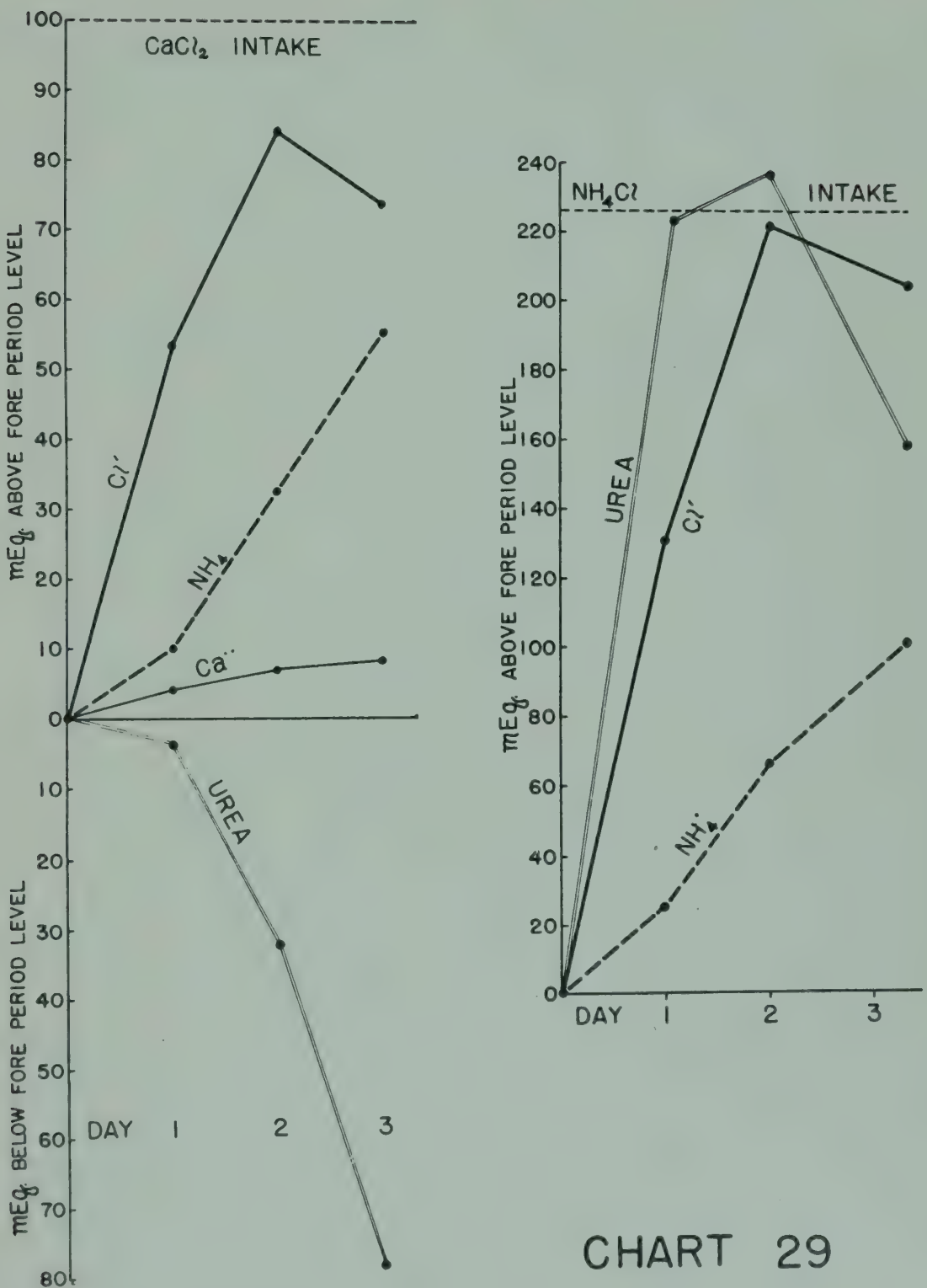

CaCl₂ INTAKE
mEq. ABOVE FORE PERIOD LEVEL
mEq. BELOW FORE PERIOD LEVEL
Cl'
NH₄
Ca''
UREA
DAY 1 2 3
NH₄Cl INTAKE
UREA
Cl'
NH₄
DAY 1 2 3

CHART 29

the result that when the limit of base economy is approached ammonium production is in full stride. The adjustments of base economy (Chart 28) are directly explained by the securely postulated but still invisible process of selective reabsorption. Motivation of ammonium production is also evidently referable to this underlying process since increments of ammonium are seen to follow reduction of pH caused by fixed base reabsorption. The connecting mechanism which produces a beautifully regulated release of ammonium is not, as yet, in view.

The quantity of urea constructed from ammonium released by deaminization processes within the body will obviously not include the ammonium taken from plasma amino acids by the kidney and placed directly in the urine. There is therefore a reciprocal relationship between urea and ammonium excretion. This is roughly described by the data in this chart, which were obtained in the course of a study of the effects of the so-called "acid producing" salts, calcium chloride and ammonium chloride, on acid-base metabolism. The neutral salt, $CaCl_2$, exerts an acid effect because relatively little of the $Ca^{\cdot\cdot}$ which it provides is absorbed from the gastrointestinal tract whereas nearly all of the Cl' is absorbed. When NH_4Cl is ingested the base NH_4 is absorbed but is immediately converted to the neutral substance urea. Both salts thus place Cl' alone in extracellular fluid and produce the requirement that the fixed base which covers it during transport to the kidney be completely returned to the plasma. The amounts of these salts which are used therapeutically produce a very large addition to the usual excess of acid over fixed base claiming excretion in the urine. Since increase in urine acidity beyond the usual value, pH 6.0, produces only a small saving of base (Chart 20), the burden of covering this large increase in acid excretion falls almost entirely on the ammonium production mechanism.

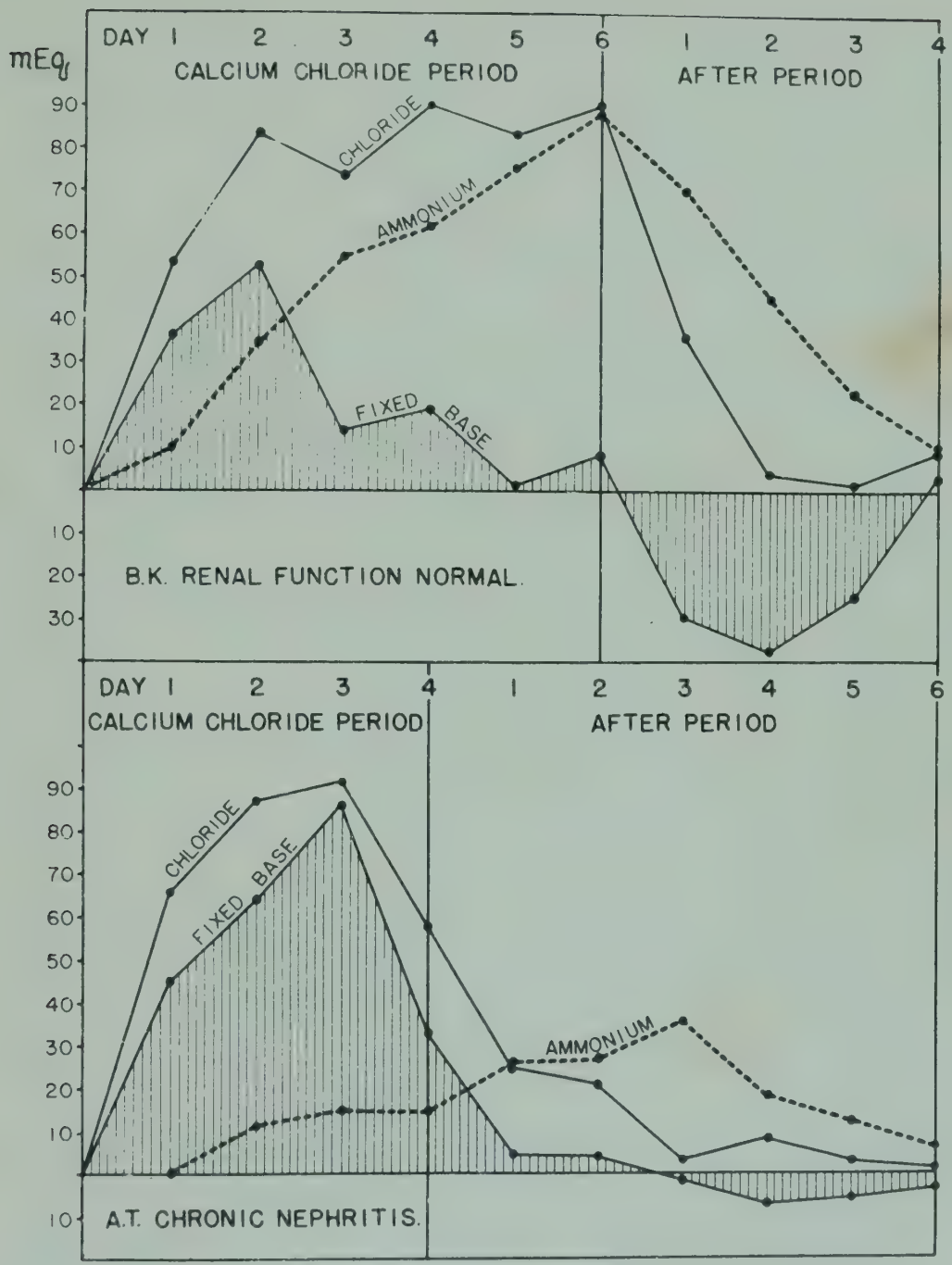
The subjects of this study were healthy individuals. They were placed on an accurately constant food intake over a considerable foreperiod during which daily excretion values for chloride, calcium, urea and ammonium were established. The values recorded in the diagrams define the extent of change with respect to the foreperiod values found on three consecutive days of addition of "acid" salt to the constant food intake. The data in the first diagram are from an eight-year-old child while receiving 100 milliequivalents of Cl' as $CaCl_2$ daily. The relatively very small quantity of the ingested base, $Ca^{\cdot\cdot}$, is seen. The Cl' increments over

the foreperiod value define the large addition to the total acid excretion. In response to this, ammonium production is extended in large steps. The values for the urea excretion, recorded in terms of potential ammonium (twice the molecular value), progressively decline in rough correspondence with the ammonium increments. The data in the other chart are from an adult who was given 226 milli-equivalents of Cl' as NH_4Cl daily. That the ingested NH_4^+ is conveyed to the kidney as urea is clearly indicated by the increase in urea excretion over the first two days. Reflection of the increasing ammonium production is not seen in these rough data over the first two days. On the third day, however, the reciprocal relationship between the urea and ammonium excretions comes into view.

An item of evidence that the locus of regulated ammonium production in the kidney is the extensive impairment of this mechanism found in chronic nephritis. This is shown by the data in this chart which were obtained by the plan of study just described. The measurements in the upper diagram are from a child with normal renal function and those in the lower diagram from a child with chronic nephritis (and edema). Both children received 100 m-eq. Cl' as $CaCl_2$ daily. The values recorded are increments over fore period levels on a constant diet. The pH of the urine over the fore periods was below 6.0 so that only slight increase in base economy was possible (Chart 20) and defense of plasma base therefore required an almost complete covering of Cl' increase by ammonium. As may be seen, even in the presence of normal renal function, ammonium response to this sudden large addition to the acid excretion is not immediately adequate. The increments of fixed base above the fore period level measure the resulting losses from the plasma. In the after period the ammonium increments surpass Cl' excretion and produce replacement of the fixed base losses. In the case of the child with chronic nephritis the ammonium response is very much slower so that, over the $CaCl_2$ period, Cl' is permitted to carry almost its entire equivalence of fixed base into the urine with negligible recovery during the after period.

Defense of the total ionic concentration of the plasma requires that a withdrawal of fixed base be accompanied by a corresponding quantity of water. This explains the diuretic action of $CaCl_2$ (and of NH_4Cl). On this premise it may be estimated that this child with chronic nephritis lost, over the four days of $CaCl_2$ ingestion, 1.4 liters of edema fluid. (Fixed base withdrawn, 220 m-eq. Fixed base in interstitial fluid, 156 m-eq./L (Chart 2). 220/156 = 1.4). As shown by this chart the diuretic effectiveness of $CaCl_2$ is greatly increased by disability of the ammonium mechanism.

Edema is a relatively infrequent event in chronic nephritis. The sluggishness of ammonium defense of plasma base produces the hazard of loss and, in consequence, the inverse change in extracellular fluid volume; dehydration. That fixed base deficit does occur in chronic nephritis has been clearly demonstrated by Peters. Additional evidence of deficit is provided by Palmer's findings that, in chronic nephritis, ingestion of a much larger



AMMONIA RESPONSE TO A LARGE ADDITION TO THE ACID EXCRETION CAUSED BY INGESTION OF CALCIUM CHLORIDE.

VALUES PLOTTED ARE INCREMENTS OVER FORE PERIOD LEVELS.

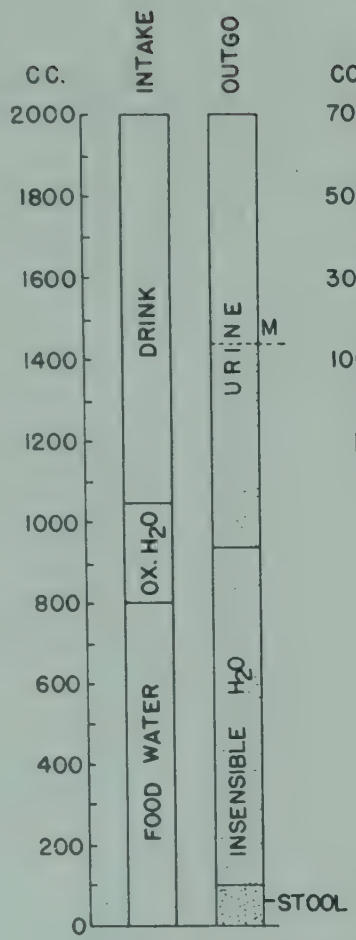
CHART 30

quantity of sodium bicarbonate is required to make the urine alkaline than in the healthy subject (the so-called alkali tolerance test). The rationale of the conventional low salt diet is therefore clearly incorrect. An ample intake of salt should be supplied.

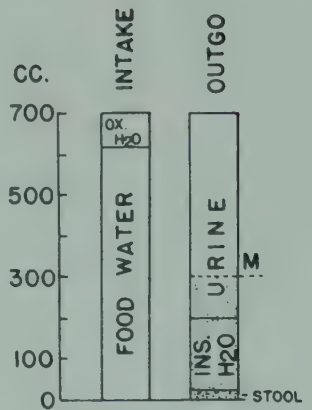
CHART 31

Water intake is composed of the water content of food, water eventually released by oxidative processes from food substances, and water drunk. Total intake is governed by the sensation of thirst. Water leaves the body in the stools, by way of the skin and lungs (insensible perspiration) and in the urine. The adjustable component of outgo is the volume of the urine. Under normal circumstances water lost in the stools is a relatively small quantity. Insensible expenditure of water is a function of the energy metabolism and serves to remove a fairly constant fraction (about 25%) of the total heat production. Adjustability of urine volume in the direction of reduction is limited by the maximal concentrating capacity of the kidney and the quantity of substances claiming excretion. Minimal water expenditure by the kidney is therefore determined by the rate of metabolism (chiefly by the metabolism of energy). Since basal energy metabolism has a linear relationship to the surface area of the body, the expenditures of water which it requires, insensible perspiration and minimal urine volume, are also determined by surface area. These expenditures derive from extracellular fluid. The volume of extracellular fluid is an approximately fixed fraction of body mass. Since body mass increases over the growth period more rapidly than surface area, there is proportionate increase in the volume of extracellular fluid with respect to rate of water expenditure and corresponding increase in security of the water balance of the body.

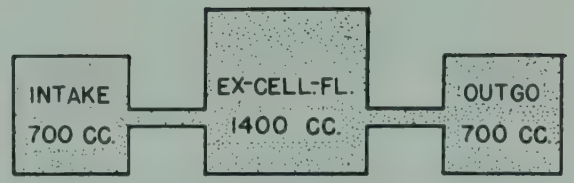
This disadvantage of being small is quantitatively illustrated by the diagrams in the chart. The components of the daily water exchange of a 70-kg. adult and a 7-kg. infant at basal levels of metabolism are shown in the columns. The relatively larger surface area of the infant prescribes a basal rate of heat production per kilogram which is approximately twice as rapid as in the adult. Insensible water loss per kilogram is therefore twice as large. In computing the values for insensible perspiration used in the diagrams, 0.5 cc./kg./hr. (Dubois) is taken for the adult and 1.0 cc./kg./hr. (Levine) for the infant. The larger energy metabolism per kilogram of the infant will also require proportionate increase in water expenditure by the kidney. Minimal urine volume is assumed to



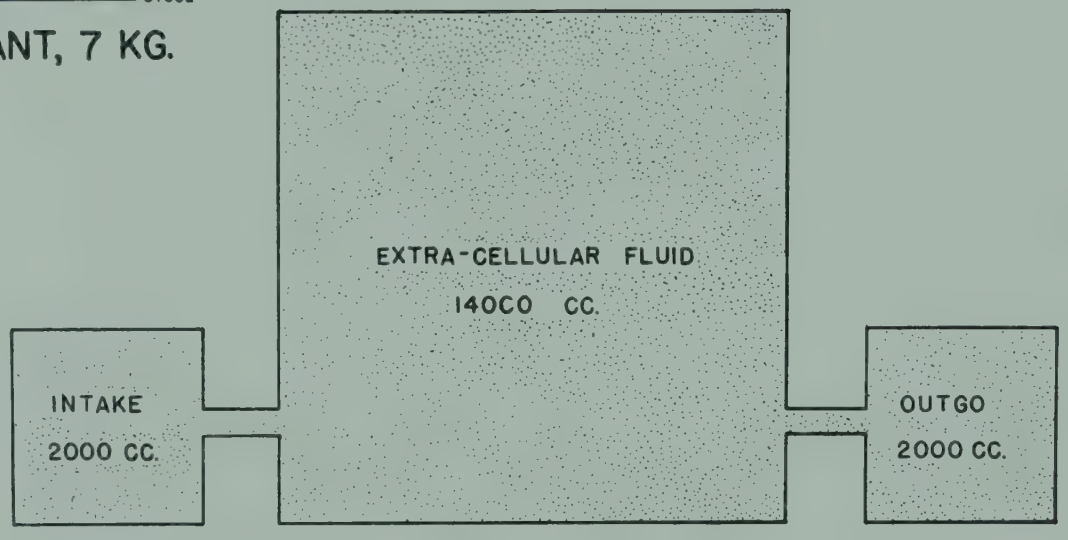
ADULT, 70 KG.



INFANT, 7 KG.



INFANT, 7 KG.



ADULT, 70 KG.

CHART 31

be 500 cc. for the adult and 100 cc., instead of 50 cc., for the infant, to cover the relatively larger excretion of end products of metabolism. The sum of the components of irreducible water expenditure (M, outgo columns) is for the infant one-fifth of the value for the ten-times-larger adult. As shown by the diagram, the usual quantity of food which a breastfed infant receives provides a wide margin of water intake beyond these relatively large obligatory expenditures.

The quantitative relationship of the water exchange to extra-cellular fluid is shown by the area diagrams. The rapidity of the exchange in the infant is at once evident. Intake is relatively large, about one-third that of the adult (column diagrams), and amounts to one-half of the volume of extracellular fluid. In the adult daily replenishment of extracellular fluid amounts to one-seventh of its volume. Water exchange of the infant is thus 3-4 times as rapid as in the adult. It is therefore not surprising that the mechanisms of control of extracellular fluid volume operate with less precision in the infant than in the adult and permit larger oscillations in day to day body weight referable to change in water balance.

Minimal water expenditure per day by the infant is 300 cc. and by the adult is approximately 1400 cc. (M, outgo columns). At these rates, in the absence of water intake, the infant's extracellular fluid would be exhausted in 5 days, and the adult's in 10 days. The infant's doubly larger surface area in proportion to body mass, by requiring corresponding increase in heat production and incidental water expenditures, thus reduces the infant's survival margin in the presence of progressive water deficit to one-half that of the adult.

CHART 32

The water balance of the body rests on volume control in the several body fluid compartments (Chart 1). The mechanics of the circulation of the blood demand a fairly stationary volume. Requirement for an approximately constant volume of intracellular fluid may also be postulated. Although the usual volume of interstitial fluid is presumably ideal for its services to the tissue cells, extensive change does not greatly disturb physiological processes. The role of interstitial fluid as the adjustable segment in the total water content of the body is clearly apparent. The advantage of its extracellular position is evident from features of

DAILY EXCRETION OF CHLORIDE AND OF WATER BY THE KIDNEY. INTAKE CONSTANT.

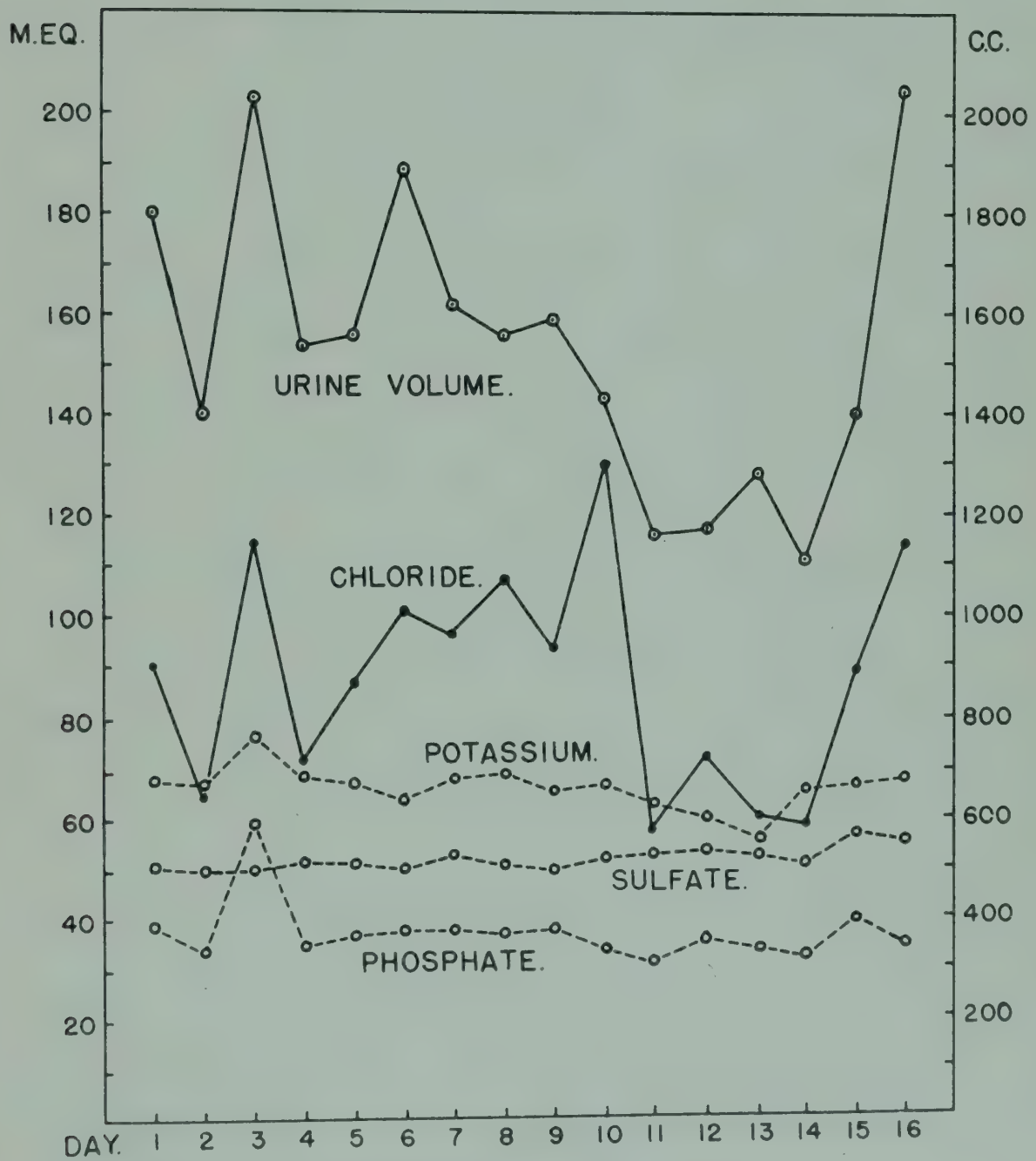


CHART 32

the water exchange. Water expenditure, in the removal of waste substances in urine and of heat by the vaporization of water, is at the expense of extracellular fluid. There is no expenditure of intracellular fluid. Actually there is a small gain of water from oxidation of food substances. The water exchange therefore consists in replacement of losses of extracellular water. Since water intake is intermittent and expenditure is continuous and of variable degree, adjustment of interstitial fluid volume is constantly required. In the presence of abnormal circumstances obstructing the water exchange, this adjustability of the interstitial compartment provides a wide survival margin. This defense of volume in the two adjacent compartments does not have the physiologically impossible attribute of rigidity. There is considerable permissible change in plasma volume and, as has been noted (Chart 14), the requirement for osmotic equality makes necessary some degree of volume adjustment between intracellular and extracellular fluid. Considering, however, that the boundaries of the body fluid compartments are elastically movable within wide limits the degree of success of the mechanisms in control of volume is very remarkable.

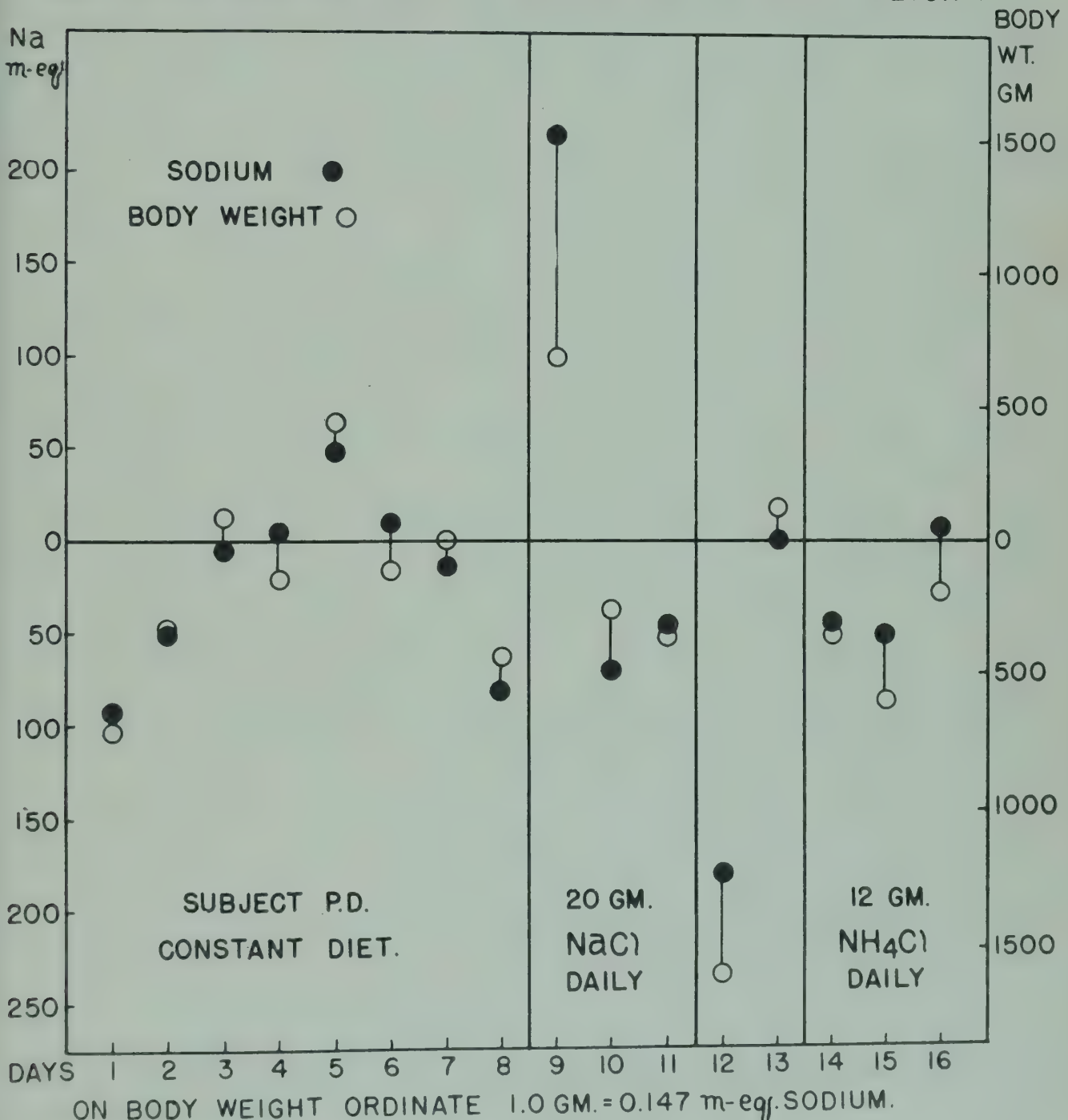
According to the above considerations, the volume of extracellular fluid, since interstitial fluid composes three-quarters of it, is necessarily fluctuant. Return to an approximately fixed value at the end of each twenty-four hour period, accomplished during the hours of sleep, might be expected. The data recorded on this chart indicate, however, a much slower process of volume control. Tne measurements (taken from a study of electrolyte metabolism by Atchley and Loeb) were obtained from consecutive twenty-four hour collections of urine from an adult on an accurately constant food and water intake. They provide indirect evidence of day to day change in the volume of extracellular fluid. This consists in the wide irregularity of the daily quantities of the extracellular ion, Cl', and the roughly stationary values for $K^{\cdot}$, HPO_4'', and SO_4'' which are large components of intracellular fluid but which are conveyed in extracellular fluid at relatively very small concentrations (Chart 2). In the presence of a constant intake of Cl' and assuming that the relatively small extrarenal excretion is approximately stationary, the irregularity of the daily quantities in urine defines fluctuation of Cl' balance. If the concentration of Cl' is held stationary in extracellular fluid, gain or loss must measure corresponding change in volume. This inference is supported by the large changes in urine volume which roughly parallel the ups and downs of Cl' excretion (the scales of the ordinates are so adjusted that m-eq:cc = 0.1:1.0, approximately the concentration of

Cl' in extracellular fluid). Change in urine volume in the presence of a fixed water intake cannot be taken as dependably measuring gain or loss of body water because of variability of the value for the large part of the water intake (1/3 - 1/2) which is removed by way of the skin and lungs. Close correlation of change in urine volume and change in Cl' excretion would therefore not be expected. Extrarenal loss of water by this subject was, however, not widely enough irregular to appreciably mask the urine volume - Cl' relationship. The data clearly permit the inference of a considerable day to day change in the volume of extracellular fluid.

Day to day change in the total water content of the body is fairly closely defined by change in body weight. A rough measurement of change in the balance of sodium, the dominant extracellular ion, can be obtained by comparing the quantity found in a twenty-four hour specimen with the average value for a period of days during which sodium intake is stationary. Irregularity in the relatively small quantity of sodium lost in the feces and by way of the skin is here ignored. The chart records daily measurements of gain or loss of body weight and of sodium, obtained from an obese subject who exhibited weight fluctuation of rather unusual degree. Food (composition and quantity) and water intake were accurately constant. After an eight-day period, body fluid adjustments were placed under unusual stress by the ingestion of 20 gm. NaCl daily for three days, and in a final period 12 gm. NH_4Cl were given daily. The scale of the sodium ordinate is so adjusted to that of body weight that 0.147 m-eq. corresponds to 1.0 gm. This is taken as the quantity of sodium in 1.00 cc. of interstitial fluid (Chart 2). If body weight loss is composed of extracellular fluid, the two measurements should fall together on the chart. Over the eight-day period of quite usual water-salt intake, there is rough agreement. On the first day of additional salt ingestion there occurs a large gain in body weight and a much larger gain in sodium. Explanation of this discrepancy between the two measurements is provided by the Darrow diagram (Chart 14). The sudden large addition to extracellular electrolyte has made necessary a transfer of water from the intracellular to the extracellular compartment. The increase in extracellular fluid volume resulting from this transfer is not registered by body weight change. Also, as seen in Chart 14, water transfer does not entirely prevent change in total electrolyte concentration. Both of these events interfere with correlation between change in water and sodium balances. By the third day of salt ingestion the measurements again coincide, indicating that the kidney has regained parallel control of water and salt. But, with abrupt cessation of the high salt intake, discrepancy again develops in the presence of a large diuresis accompanied by a larger loss of sodium.

These data make it clear that under ordinary circumstances change in water balance (as defined by body weight) is almost entirely referable to change in volume of extracellular fluid. When, however, extensive adjustment by water transfer is necessary, change in water balance does not closely follow change in extracellular fluid volume. This is more nearly defined by change in sodium balance, but with an unsatisfactory accuracy because of appreciable

DAY TO DAY GAIN OR LOSS OF SODIUM AND OF BODY WEIGHT.



ON BODY WEIGHT ORDINATE 1.0 GM. = 0.147 m-eq. SODIUM.

CHART 33

change in sodium concentration. Moreover the effect of another event, a large increase in the excretion of the intracellular base, potassium, during the periods of salt ingestion, must be appraised. In the next chart a description of body fluid changes in this subject, taking into account these several variables, is presented.

The following table gives the measurements from which are derived the data recorded in this chart and in the two charts which follow it.

CHART 33 (Continued)

	Day	Body Wt. gm.		Sodium, m-eq.		Potassium, m-eq.	
		97386	±	in urine.	±93*	in urine.	±61.4
	1	96696	-690	186	-93	59.9	+ 1.5
	2	96386	-310	141	-48	66.9	- 5.5
	3	96506	+120	97	- 4	64.5	- 3.1
	4	96336	-170	86	+ 7	69.9	- 8.5
	5	96786	+450	42	+51	53.2	+ 8.2
	6	96676	-110	80	+13	54.8	+ 6.6
	7	96676	± 0	107	-14	57.8	+ 3.6
	8	96226	-450	175	-82	64.3	- 2.9
20 gm. NaCl.	9	96896	+670	220	+218	74.9	-13.5
	10	96676	-220	509	-71	89.5	-28.1
	11	96336	-340	484	-46	72.8	-11.4
	12	94746	-1590	273	180	52.8	+ 8.6
	13	94866	+120	94	- 1	40.6	+20.8
12 gm. NH_4Cl	14	94526	-340	138	-45	89.0	-17.6
	15	93976	-550	144	-51	133.0	-71.6
	16	93726	-250	86	+ 7	100.0	-38.6

* This quantity is taken as the daily intake of Na exclusive of the small portion lost by way of the feces and skin. It is obtained from the total excretion in urine over the 8-day fore period corrected for Na lost from the body (Total Na excretion in urine, 914 m-eq. Total body weight loss, 1160 gm. 1160 x 0.147 = 170 m-eq. Na. 914-170 = 744. 744/8 = 93.) During the period of NaCl ingestion the daily intake of Na regulatable by the kidney becomes 93 + 345 = 438 m-eq.

The body fluid dimensions displayed by the Darrow-Yannet diagram (Chart 14) may be designated as follows:

E_e = Electrolyte content of extracellular fluid, milliosmols

E_i = Electrolyte content of intracellular fluid, milliosmols

C = Electrolyte concentration, milliosmols per liter

V_e = Volume of extracellular fluid, liters

V_i = Volume of intracellular fluid, liters

Equality of C in extracellular and intracellular fluid is assumed on the premise of attainment of osmotic equilibrium.

The data used in constructing the chart are derived from the daily measurements of change in body weight and in the balances for Na and K, given in the table on the preceding page, on the basis of the following assumed values for body fluid dimensions at the outset of the period of study: V_e = 16 (found by the thiocyanate method), V_i = 32 (50% of pre-obesity body weight), C = 310 (Chart 2), E_e = 4960 (16 x 310), E_i = 9920 (32 x 310). Change in body weight is taken as measuring change in total body fluid, $V_e + V_i$, and the balance changes found for Na and K (x 2 to provide anion equivalents) are used to define change in E_e and E_i respectively. The observed data thus permit estimation of V_e and V_i together and of E_e and E_i separately. Values for C, V_e and V_i are then derived as follows:

$$E_e + E_i/V_e + V_i = C,\ E_e/C = V_e,\ E_i/C = V_i.$$

The day by day changes found for C, V_e, and V_i by this process of estimation are recorded additively across the 16-day period of study.

Over the first 8 days, although NaCl intake is stationary at a usual value, extracellular fluid exhibits a large and slow moving fluctuation which corresponds closely with change in body weight. The slight extent of adjustment by water transfer is shown by the small oscillations of intracellular fluid volume. But with a large and abrupt increase of NaCl intake extensive transfer of intracellular water occurs. This accounts for the increase of extracellular fluid volume beyond the observed gain in body weight.

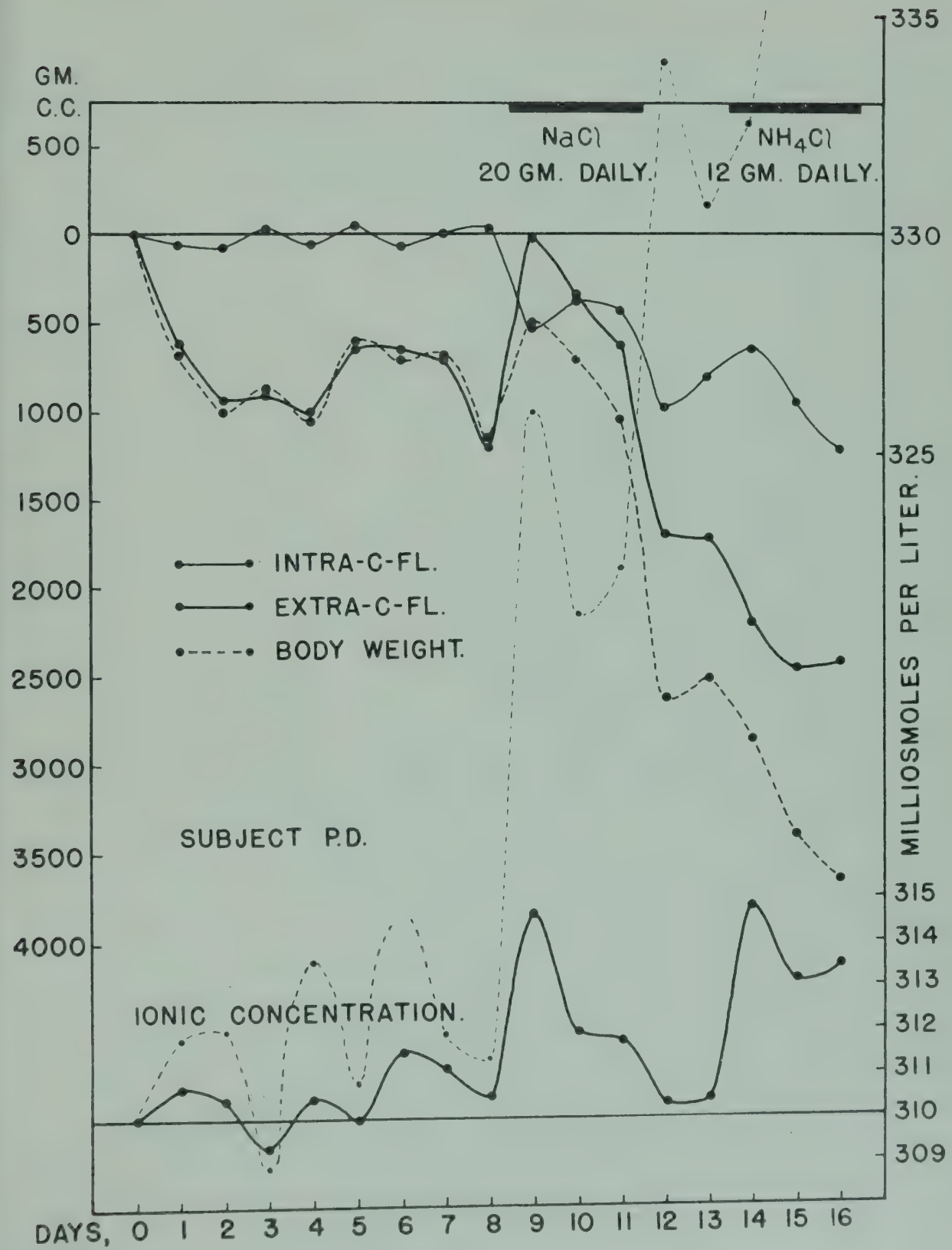

GM.
C.C.
500
0
500
1000
1500
2000
2500
3000
3500
4000
NaCl
20 GM. DAILY.
NH4Cl
12 GM. DAILY.
INTRA-C-FL.
EXTRA-C-FL.
BODY WEIGHT.
SUBJECT P.D.
IONIC CONCENTRATION.
335
330
325
315
314
313
312
311
310
309
MILLIOSMOLES PER LITER.
DAYS, 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

CHART 34

CHART 34 (Continued)

In the lower part of the chart the calculated values for total electrolyte concentration are recorded. They show the excellent defense of the usual concentration level. Even during the periods of stress produced by salt ingestion, departure is only to the extent of 4 - 5 milliosmols per liter from the usual value of 310. The broken line shows the change in extracellular electrolyte concentration which would have occurred in the absence of adjustment by water transfer.

CHART 35-A

The daily values for excretion of potassium in urine are given in the upper section of the chart. They show extensive increments during the periods of salt ingestion. In the lower section, the calculated values for total ionic concentration in the body fluids, seen in the preceding chart, are again recorded. If the change in potassium excretion is omitted from the calculation of total ionic concentration, the values estimated from sodium excretion alone produce the broken line on the chart. A relationship of removal of intracellular electrolyte to preservation of the normal total ionic level is clearly evident. Following the rise in concentration at the outset of each of the periods of salt ingestion a return toward the usual value is seen to coincide with an increased excretion of potassium. From this chart and the preceding one it is evident that neither the volume nor total electrolyte of intracellular fluid is maintained independently of events occurring in extracellular fluid.

CHART 35-B

The lag in renal removal of a large load of sodium placed in the extracellular fluid compartment by intravenous infusion of an isotonic solution of sodium chloride and the resulting expansion of extracellular fluid volume which preservation of the normal sodium concentration requires is excellently shown by data from Stewart and Rourke presented in the chart. Very large infusions, averaging 6.7 liters daily, were given an adult patient over a 4-day period following a brief surgical procedure under ether anesthesia. The average daily quantity of NaCl thus provided was approximately 60 gm. Measurements of the sodium exchange expressed as milliequivalents were as follows:

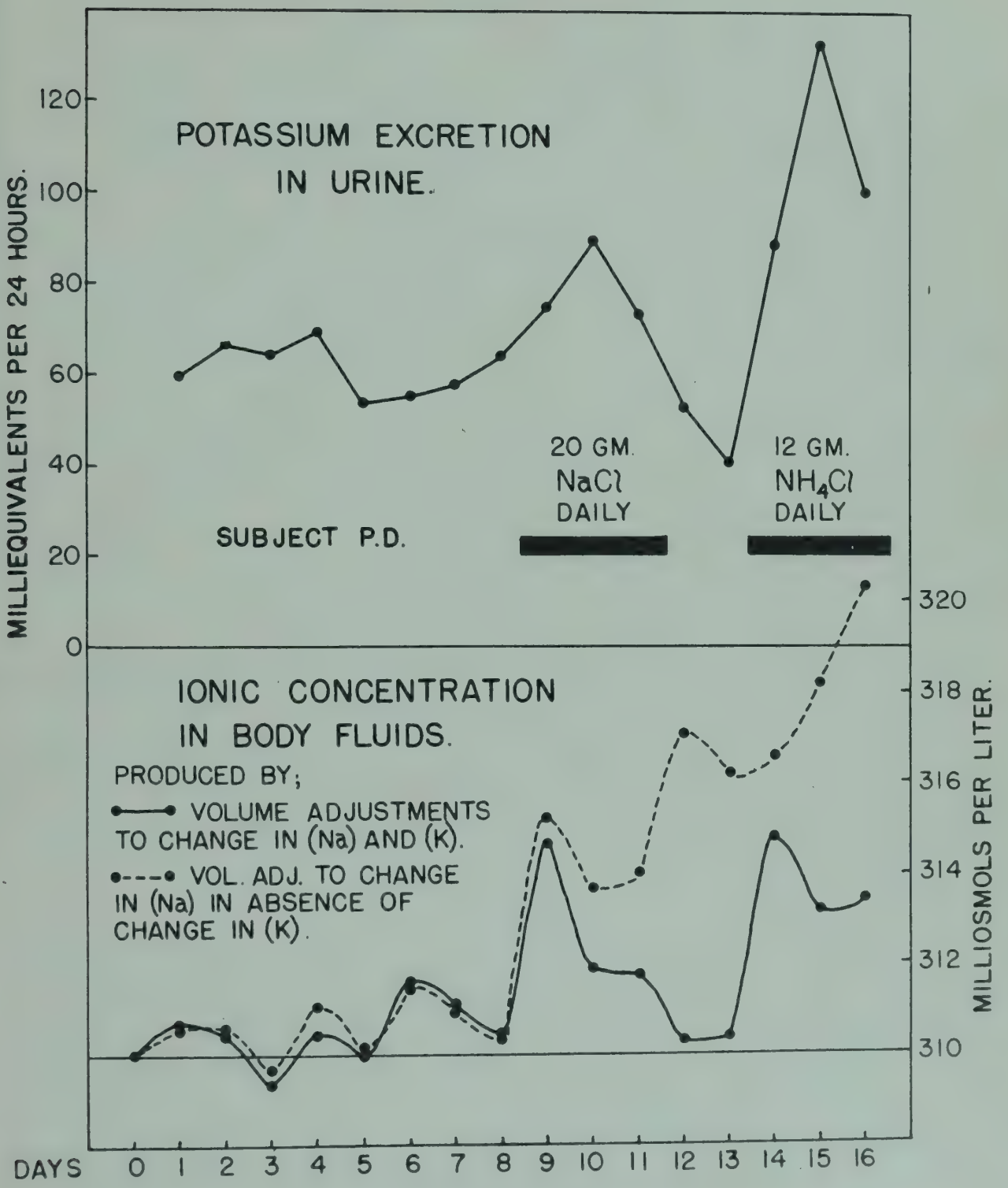

POTASSIUM EXCRETION
IN URINE.
MILLIEQUIVALENTS PER 24 HOURS.
120
100
80
60
40
20
0
20 GM.
NaCl
DAILY
12 GM.
NH4Cl
DAILY
SUBJECT P.D.
IONIC CONCENTRATION
IN BODY FLUIDS.
PRODUCED BY;
VOLUME ADJUSTMENTS
TO CHANGE IN (Na) AND (K).
VOL. ADJ. TO CHANGE
IN (Na) IN ABSENCE OF
CHANGE IN (K).
320
318
316
314
312
310
MILLIOSMOLS PER LITER.
DAYS
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

CHART 35-A

CHART 35-B (Continued)

Day	Intake	Urine	Balance	Cumulative
1	869	414	+ 455	+ 455
2	1000	651	+ 349	+ 804
3	1225	1017	+ 208	+1012
4	1032	1229	- 197	+ 815

The data describe gradual adjustment of outgo to load; not until the 4th day does outgo exceed intake and cumulative retention begin to decline. The accuracy of defense of Na concentration is shown by plasma values found at the beginning and end of the period of study; 140 and 139 meq. Na/litre respectively.

The chart shows the large addition to the initial volume of extracellular fluid produced by surplus sodium. There was roughly corresponding increase in plasma volume. Total plasma protein was also found to increase to an extent which prevented large fall in protein concentration. The normal circulation of extracellular fluid between the vascular and interstitial compartments was thus sustained so that there was no edema in spite of the large increase in the volume of extracellular fluid.

These data make it clear that, when isotomic sodium chloride solution is used therapeutically, the kidney cannot be expected to prevent overhydration by immediately removing surplus sodium. The extensive overhydration of this subject produced no observable physiological disadvantage. It is probable, however, that this might not be the case for a severely sick patient. Appraisement of the fluid replacement requirement is therefore necessary in the treatment of dehydration.

The ability of the kidney to defend the normal ionic concentrations of plasma by rapidly removing a very large water load is shown by data from a patient receiving large infusions of a 5% solution of glucose. A small decline in extracellular fluid volume is found which is referable to the inability of the kidney to completely prevent removal of sodium in the urine. Sodium concentration in urine is lowered below the plasma level to presumably the limit permitted by available osmotic work (Chart 17-F). This limit, as found for this subject is 9 meq./liter; an approximately 16-fold reduction of the normal plasma concentration. The large urine volume, approximately 5 liters daily, therefore produces removal of an appreciable quantity of sodium. The degree of defense of plasma (Na) is shown by measurement obtained at the beginning and end of the 4-day period; 137 and 133 meq./liter respectively.

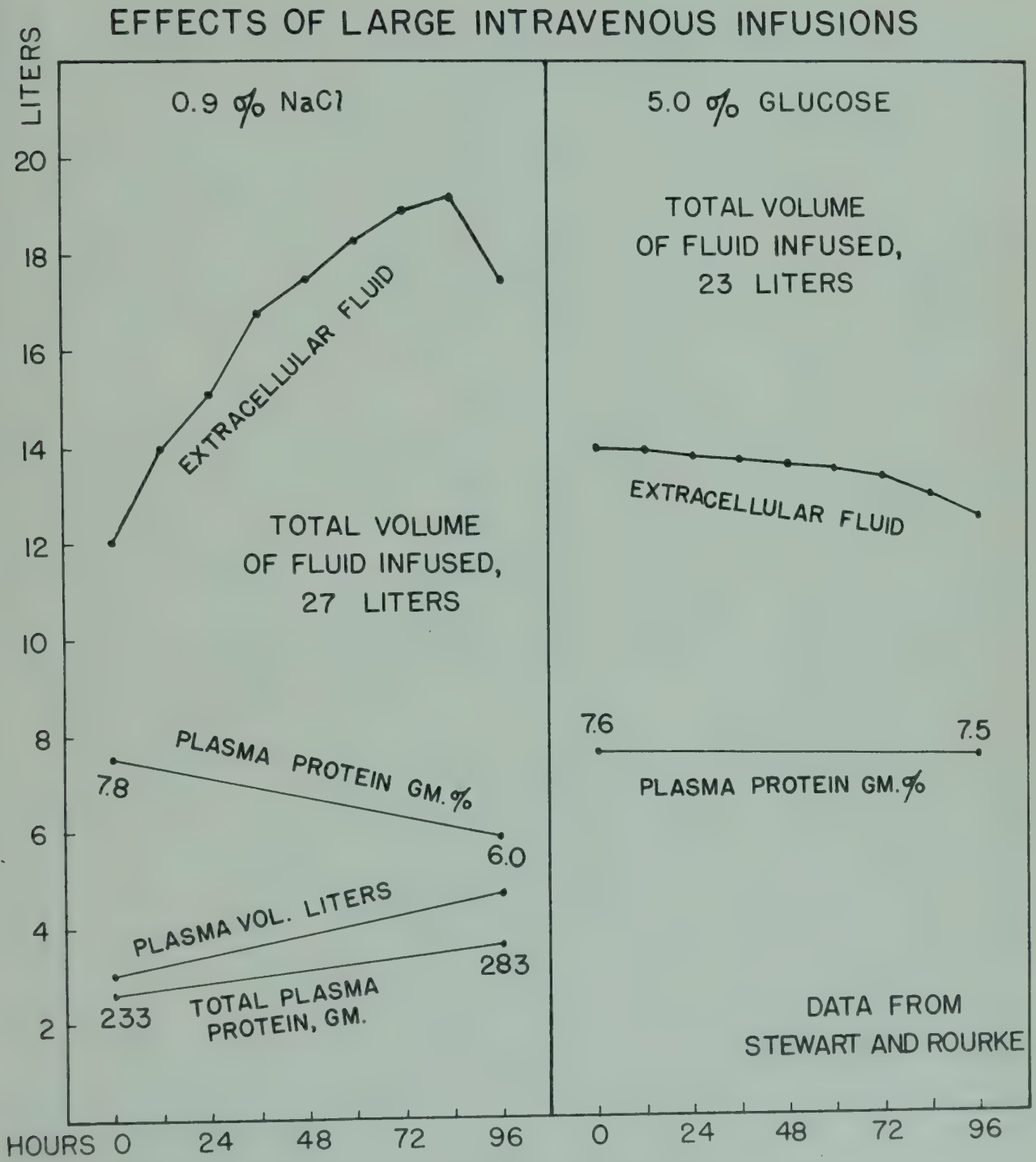

EFFECTS OF LARGE INTRAVENOUS INFUSIONS
LITERS
20
18
16
14
12
10
8
6
4
2
0.9 % NaCl
5.0 % GLUCOSE
EXTRACELLULAR FLUID
TOTAL VOLUME
OF FLUID INFUSED,
27 LITERS
TOTAL VOLUME
OF FLUID INFUSED,
23 LITERS
EXTRACELLULAR FLUID
PLASMA PROTEIN GM.%
7.8
6.0
7.6
7.5
PLASMA PROTEIN GM.%
PLASMA VOL. LITERS
283
233
TOTAL PLASMA
PROTEIN, GM.
DATA FROM
STEWART AND ROURKE
HOURS 0 24 48 72 96
0 24 48 72 96

CHART 35-B

The normal total ionic concentration of the body fluids is so successfully sustained by renal regulation that even in the presence of drastically abnormal circumstances extensive reduction is a rare event. In the situation described by the chart there was complete absence of renal control. The data are from an infant exhibiting anuria over a period of 6 days following administration of a sulfa drug. In the state of anuria water is removed from the body by way of the lungs and skin at a nearly constant rate, which for a 10 Kg. infant is about 250 cc. daily. The infant was given water (glucose solution) in large excess over this fixed expenditure. On the fifth day of anuria symptoms of so-called water intoxication appeared and extensive hypotonicity of the body fluids was shown by the concentration values found for plasma Na, Cl, and HCO_3, recorded in the chart.

The normal values for total solute concentration (ordinate) the volume of extracellular and of intracellular fluid (abcissa), are shown in the top diagram. The solute content of the body fluids is also recorded. The extent of reduction of total ionic concentration (middle diagram) is computed from the normal and found values for (Na). The volume producing this reduction is obtained by dividing total solute content (620 + 1550) by the value found for concentration. A relatively very large addition to body water, 2200 cc. is thus defined. This water is distributed in proportion to the solute content of extracellular and intracellular fluid.

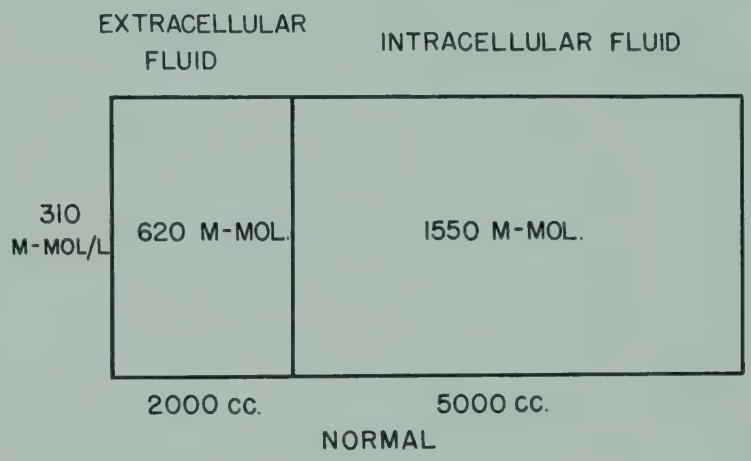
The predicament of hypotonicity in the presence of anuria can be solved only by providing an hypertonic solution of electrolyte. This was undertaken by infusion of 1.8% NaCl solution. The quantity of twice isotonic solution required to restore normal concentration is obviously equivalent to the addition of water which caused the reduction; 2200 cc. Since extracellular electrolyte is used, water will be transferred from the intracellular compartment as the concentration in extracellular fluid is raised, with final restoration of the normal volume of intracellular fluid (bottom diagram). The initial body water surplus is thus placed entirely in the extracellular compartment along with the water provided by NaCl solution. The resulting enormous expansion of extracellular fluid volume shown in the diagram is probably far beyond the physiologically permissible limit. In the instance of this patient there was, fortunately, a spontaneous recovery of renal function with rapid restoration of normal ionic concentration before more than a small part of the theoretical requirement for 1.8% NaCl solution could be provided.

HYPOTONICITY FROM OVERHYDRATION

DATA FROM

10 KG. INFANT

ILLUSTRATING EFFECTS OF INFUSION OF GLUCOSE SOLUTION IN THE PRESENCE OF ANURIA



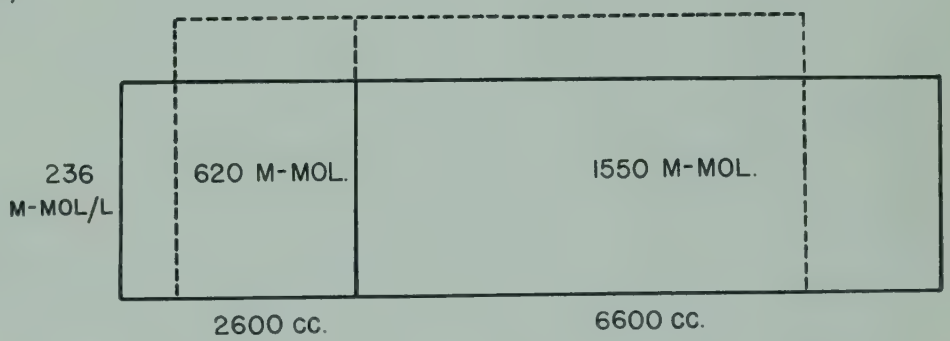
NORMAL

HYPOTONICITY

PLASMA Na, 108 M-MOL/L
" Cl, 67 "
" HCO_3, 21 "
108 ÷ 142 x 310 = 236 "

OVERHYDRATION

SOLUTES, 2170 M-MOL.
2170 ÷ 236 = 9.2 LITERS
- 7.0 "
VOLUME, + 2.2 "



REPAIR BY 1.8% NaCl SOLUTION

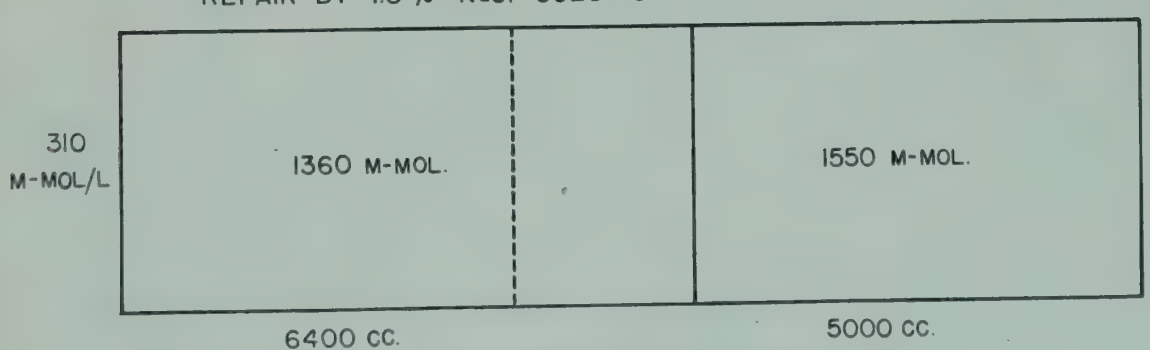


CHART 35-C

Loss of body fluid is described by the term dehydration. An important feature of any process of dehydration is that the water loss is always accompanied by a loss of electrolyte. When water deficit from inadequacy of intake is the primary event, preservation of the normal ionic concentration of the body fluids requires removal of a corresponding quantity of electrolyte. Conversely, when electrolyte is withdrawn an accompanying removal of water is necessary to the same end. Loss of gastro-intestinal secretions and of sweat remove water and electrolyte together. Dehydration is therefore an incomplete term since it does not indicate the accompanying loss of electrolyte. A therapeutic corollary of fundamental importance is that dehydration cannot be repaired by water alone; the lost electrolyte must also be replaced.

Initial defense of the organism in the presence of a process of dehydration is directed toward support of the volume of the blood plasma and protection of the volume of intracellular fluid at the expense of interstitial fluid. Preservation of the normal ionic concentration by adjustment of electrolyte removal to water loss, or vice versa, is also undertaken. When the progress of dehydration is rapid, attainment of these ends is incomplete. Ionic concentration departs progressively from its normal value. As was first observed by Kerpel-Fronius, ionic concentration rises when loss of water is the initial event and falls when dehydration results from withdrawal of electrolyte. This is clearly shown by the values for plasma(Na) from a thirsting dog and from a dog dehydrating after an experimental obstruction of the pylorus; Figures 1 and 4. These changes in (Na) suggest a lag in volume-electrolyte adjustment. The severe secondary impairment of renal function which dehydration causes supports this surmise.

There is also with advancing dehydration loss of intracellular fluid. Figure 2 records, over the 15-day survival period of a thirsting dog, body fluid losses estimated from measurements of body weight change, of Na, K, and N excreted in urine, and of plasma (Na). As shown by the shaded regions, extra- and intra-cellular fluid losses are, for the entire survival period, about equal. In other words, about one-half of the expenditure of extracellular water is replaced by water from the intracellular compartment. As shown in the diagram, this contribution has several components: A is water released by consumption of protoplasm incidental to fasting; B, water transferred from the intracellular compartment under the osmotic effect of the increase in extracellular ionic concentration (chart 14); C, additional transfer of water from further

increase in the osmotic gradient by removal and excretion of intracellular electrolyte,K, beyond the quantity released by consumption of protoplasm. Without this replenishment, as shown in the diagram by the values for total water expenditure,extracellular fluid would have been completely removed. It is thus evident that although the interstitial portion of extracellular fluid is in large part expendible and constitutes the first line of defense against processes of dehydration,intracellular fluid must also be used to the physiologically permissible limit if maximum width of survival is to be gained. That the brunt of dehydration falls first on interstitial fluid may be seen in the record of extracellular fluid loss; 80% occurs during the first third of the survival period. Whatever the cause of (Na) increase and of preferential excretion of K, these changes from the normal pattern are, in effect, defensive adjustments which greatly extend survival. The rapidly progressive restriction of extracellular fluid loss which they together accomplish is clearly shown by the curve for Na excretion (figure 3). According to these data the physiological limitof volume reduction is for extracellular fluid 60% and for intracellular fluid 30%.

In dehydration caused by continued vomiting of stomach secretions there is a direct loss of Na. There is also a direct, and relatively larger, loss of water in the secretions, to which is added the obligatory expenditures of water by the skin and lungs and the limited use of water by the kidney. There is thus withdrawal from extracellular fluid of water in excess of Na, which should cause an increase in the concentration of Na. Loss of electrolyte (determined by loss of Na) therefore cannot be regarded as the leading event. It will, however, determine the extent of reduction of extracellular fluid volume provided that water can be found to provide the usual concentration value for Na. Water is supplied, and in actual surplus of this requirement,as shown by the progressive decrease in(Na), figure 4. Considerable replacement of extracellular water loss by water from the intracellular compartment is thus evident. To attempt to explain this water transfer in terms of the processes operative in dehydration from thirsting(figure 2): Increase in extracellular electrolyte (B) can have only an initial effect. Owing to the much shorter survival period the quantity of water released by the consumption of protoplasm(A) will be relatively small. So that apparently the mysterious mechanism of K removal (C) must account for the greater part of the water taken from the intracellular compartment. Dehydration from loss of digestive secretions has not been given the beautifully complete description which Elkinton and Taffel's measurements provide for body fluid

losses from water deprivation. A large excretion of K has, however, been found. The rapid acceleration of dehydration when loss of water and electrolyte in digestive secretions is added to the obligatory expenditures defined by the data for thirsting is shown by the much shorter survival period of the animal with pyloric obstruction.

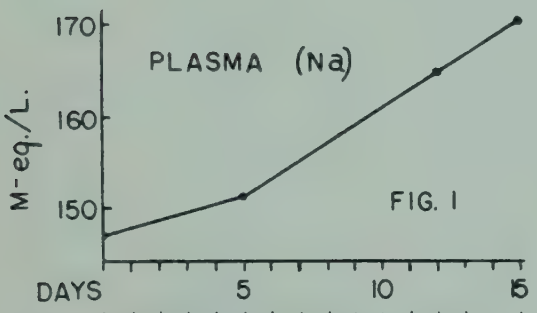
CHART 36-B

Rapid dehydration will be produced by circumstances which require excessive vaporization of body water in defense of body temperature, unless prevented by equivalent increase of water intake. Over the range of environmental temperature within which comfort can be gained by adjustment of clothing, approximately one-quarter of the heat produced within the body is removed by the vaporization of water brought to the surface of the skin and lungs by an apparently passive process of diffusion. This water composes the so-called insensible water loss. The remainder of heat production is removed by radiation, conduction and convection. As environmental temperature approaches body temperature the rate of heat transfer by these processes is reduced. This reduction becomes progressively rapid when environmental temperature rises above 80°F and produces the requirement for a corresponding increase of heat removal by the vaporization of body water. Water beyond the insensible water loss is provided as sweat. High humidity will reduce the rate of vaporization of sweat and increase the quantity required.

The hazard of dehydration by vaporization of body water is illustrated by the data in the chart which record the results of experiments undertaken with the purpose of roughly defining the extent of excessive vaporization of body water and the effectiveness of preventive measures under conditions to which men on a life raft would be exposed in hot weather. The measures used in these experiments were: reduction of environmental temperature by provision of shade; promotion of conduction by periodic immersion in the sea; increase of the cooling effect of breeze (promotion of convection) by removal of clothing; and vaporization of sea water in place of body water by wetting clothing with sea water. In order to permit observation of the separate effects of these measures, the raft on which the subjects reclined was provided on all sides with a cloth screen which almost completely excluded the cooling effect of breeze. The measurements of insensible water loss + sweat were obtained by weighing the subjects nude at the beginning and at the end of 5-8

WATER DEPRIVATION

DOG - THIRSTING



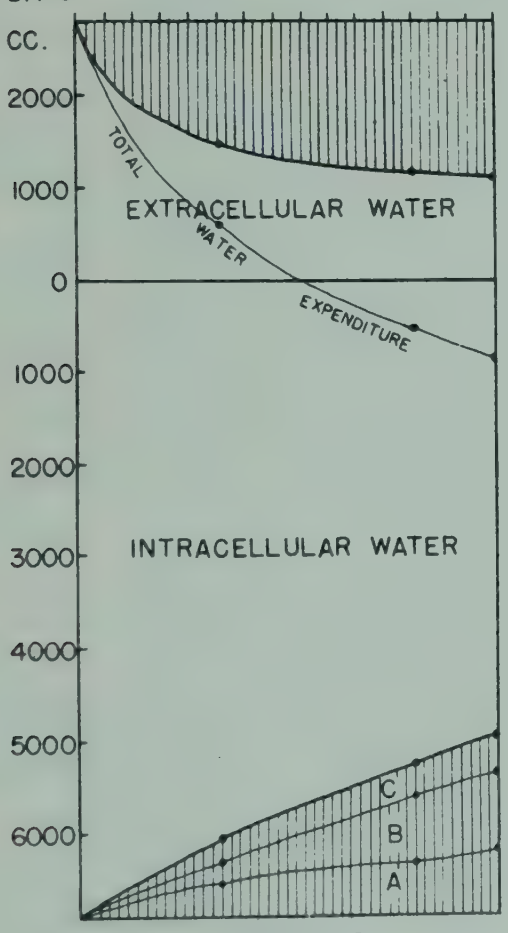


FIGURE 2

LOSS OF ELECTROLYTE

DOG - PYLORIC OBSTRUCTION

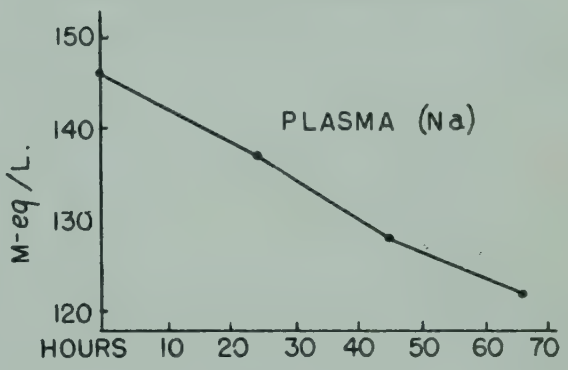
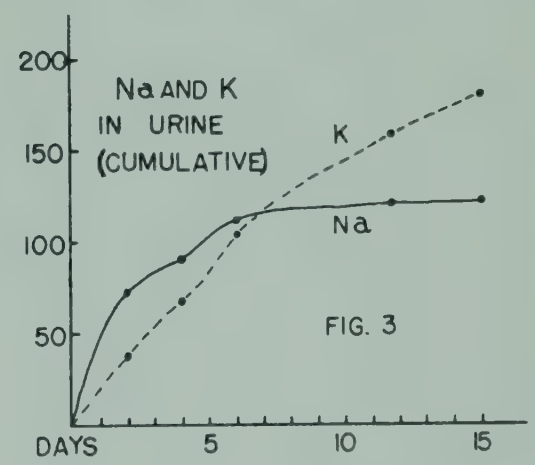


FIGURE 4



DATA FOR FIGURES 1, 2 AND 3
FROM ELKINTON AND TAFFEL

CHART 36-A

hr. periods and measuring in terms of weight the irtake of water and food and the outgo of urine. The insensible loss of body weight, as defined by Body Wt. Loss + Wt. Food and Water Intake - Wt. Urine, was taken as measuring extra-renal water loss. The values found for the individual subjects are shown in the chart by the black columns. The broken line across the chart defines the basal or irreducible insensible water loss as 0.6/Kg/hr. This value is the average of measurements obtained from the individual subjects over an 8-hr. period ashore and in shade, the subjects being at rest, clothed and comfortably cool. Shade on the raft was provided by a large umbrella. Shade temperature is recorded on the chart and also measurement by a globe thermometer taken in the sun which serves to define roughly the increase of environmental warmth above the shade temperature referable to direct solar radiation.

The data from these experiments give quantitative illustration of the relatively enormous expenditure of body water which is required when environmental temperature rises above body temperature and the burden of cooling falls entirely on heat removal by vaporization of water. Expenditure of water by subject J was ten times the basal requirement. The values from the other subjects describe the effectiveness of the simple measures employed to prevent this large wastage of body water. It may be noted that the quantity of water lost by subject J over the 6-hr. period was 2400 cc., which is several times the daily water intake requirement for a castaway estimated on the premise of preservation of basal insensible expenditure (Chart 45). The cooling effect of breeze is strikingly shown by the complete defense of the basal rate of water vaporization found for subject J when, in a subsequent experiment, he sat unclothed in a row boat and exposed to light breeze.

Moderate sweating by bed patients is not easy to observe. These data suggest that sweating may add to water outgo to an unappreciated extent.

The increased heat production by physical activity of more than moderate extent requires vaporization of sweat for complete removal. When heavy work is done in a hot environment the volume of sweat becomes very large. Dill in his studies at Boulder Dam found body water expenditures of 8-10 liters daily. Since sweat contains appreciable quantities of sodium and chloride, replacement of the losses of extracellular fluid requires provision of sodium chloride as well as water.

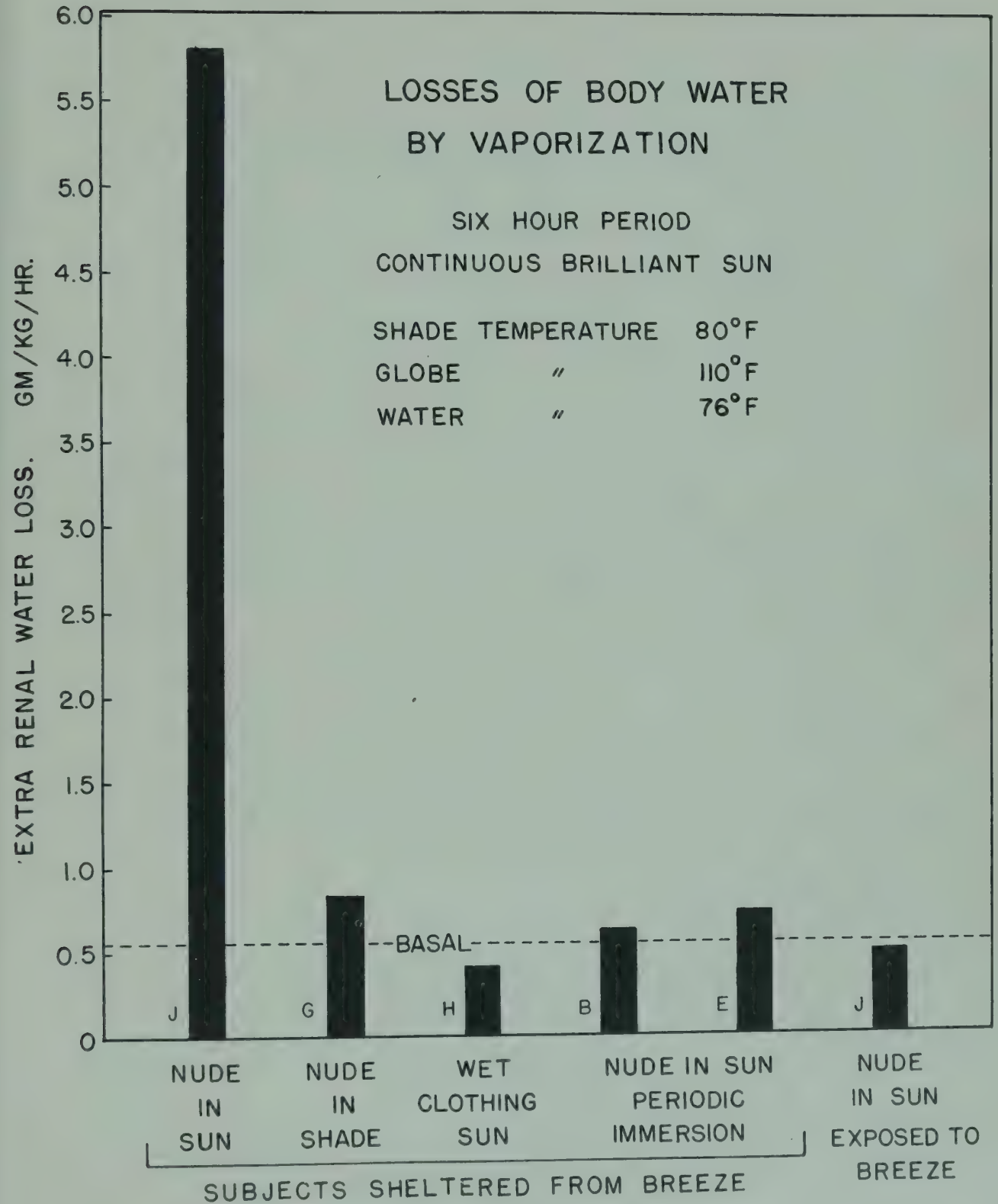

LOSSES OF BODY WATER
BY VAPORIZATION
SIX HOUR PERIOD
CONTINUOUS BRILLIANT SUN
SHADE TEMPERATURE 80°F
GLOBE " 110°F
WATER " 76°F
EXTRA RENAL WATER LOSS. GM/KG/HR.
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
BASAL
J
G
H
B
E
J
NUDE IN SUN
NUDE IN SHADE
WET CLOTHING SUN
NUDE IN SUN PERIODIC IMMERSION
NUDE IN SUN EXPOSED TO BREEZE
SUBJECTS SHELTERED FROM BREEZE

CHART 36-B

Clinically, much the most frequent cause of severe dehydration is disturbance of gastro-intestinal function to the extent of producing continued vomiting or diarrhoea. The gastro-intestinal secretions, aside from their enzyme content, are constructed from water and electrolytes taken from the blood plasma. Under normal circumstances, these materials are reabsorbed. Interference with their return to the plasma will therefore cause a progressive withdrawal of extracellular fluid. That loss of gastro-intestinal secretions is a quantitatively adequate explanation of extensive dehydration is clearly evident from the values given in this chart for the quantities of these secretions produced in twenty-four hours. Together they produce a total volume which is more than twice that of blood plasma or nearly two-thirds of the interstitial reserve. It is thus evident that interference with this circulation of water and electrolytes between the gastro-intestinal tract and the vascular compartment will set up a rapid process of withdrawal of extracellular fluid. Moreover circumstances which produce wastage of gastro-intestinal secretions usually also more or less interfere with fluid intake, so that there is additional water loss from failure of replacement of expenditures by the kidneys, lungs and skin.

TOTAL VOLUME OF DIGESTIVE SECRETIONS PRODUCED IN 24 HRS BY ADULT OF AVERAGE SIZE

SALIVA,	1500 cc.
GASTRIC SECRETIONS,	2500 cc.
BILE,	500 cc.
PANCREATIC JUICE,	700 cc.
SECR. OF INTESTINAL MUCOSA,	3000 cc.
	8200 cc.
BLOOD PLASMA VOLUME,	3500 cc.

CHART 37

In these diagrams the relative amounts of sodium, chloride ion, and bicarbonate ion in the digestive secretions are shown. The sums of the other anion and cation components are indicated at the foot of their respective columns. These remainders are estimated from incomplete data but are probably near the values given. The total quantity of electrolyte in the secretions, as shown by the heights of the diagrams is closely the same as in blood plasma. Also, as in plasma, the large components of their structure are ($Na^{\cdot}$), ($Cl^{\prime}$) and ($HCO_3^{\prime}$). The diagrams make clear that failure of reabsorption of these secretions will withdraw water and total electrolyte from extracellular fluid in approximately plasma proportions and that the significant electrolyte loss will be almost entirely composed of sodium and chloride ion; the bicarbonate ion in the secretions, derives from the circumambient $H.HCO_3$ and has no relationship to ($HCO_3^{\prime}$) in extracellular fluid.

The important feature of the composition of these secretions from the point of view of structural change in extracellular fluid is departure of the ($Na^{\cdot}$):($Cl^{\prime}$) ratio from its plasma value. This is conspicuous in gastric juice and in pancreatic juice; in the other secretions the relative quantities of $Na^{\cdot}$ and $Cl^{\prime}$ are roughly the same as in plasma. It is clear from the diagram of the gastric juice that loss of this secretion will cause a much more rapid withdrawal of $Cl^{\prime}$ than of $Na^{\cdot}$ from plasma. It is probable that actually there is no Na in the acid secretion from the digestive glands of the stomach. The small quantity shown in the diagram may be explained by admixture of the alkaline secretion of the gastric mucosa, the composition of which is described by the next diagram. The specimen from which these measurements were obtained was taken from an isolated pouch constructed in the pyloric antrum, in which region there is no secretion of the true juice. Ordinarily the relative quantity of this secretion is small, but in the presence of irritative conditions which provoke vomiting it becomes much larger and may reach a volume of about one-half that of gastric juice. There is therefore, with vomiting, a loss of $Na^{\cdot}$ which may be approximately one-half the loss of $Cl^{\prime}$. Because of the dominating relationship of $Na^{\cdot}$ to total ionic content of extracellular fluid (Chart 6), it is this loss of Na which is significant as regards extent of dehydration. Diarrhoea causes loss of pancreatic juice which contains $Na^{\cdot}$ in much larger excess of $Cl^{\prime}$ than plasma. Gastric juice, and all of the other intestinal secretions are, however, also exposed to loss, so that $Na^{\cdot}$ and $Cl^{\prime}$ are withdrawn in roughly their plasma proportions.

ELECTROLYTE COMPOSITION OF GASTRO-INTESTINAL SECRETIONS

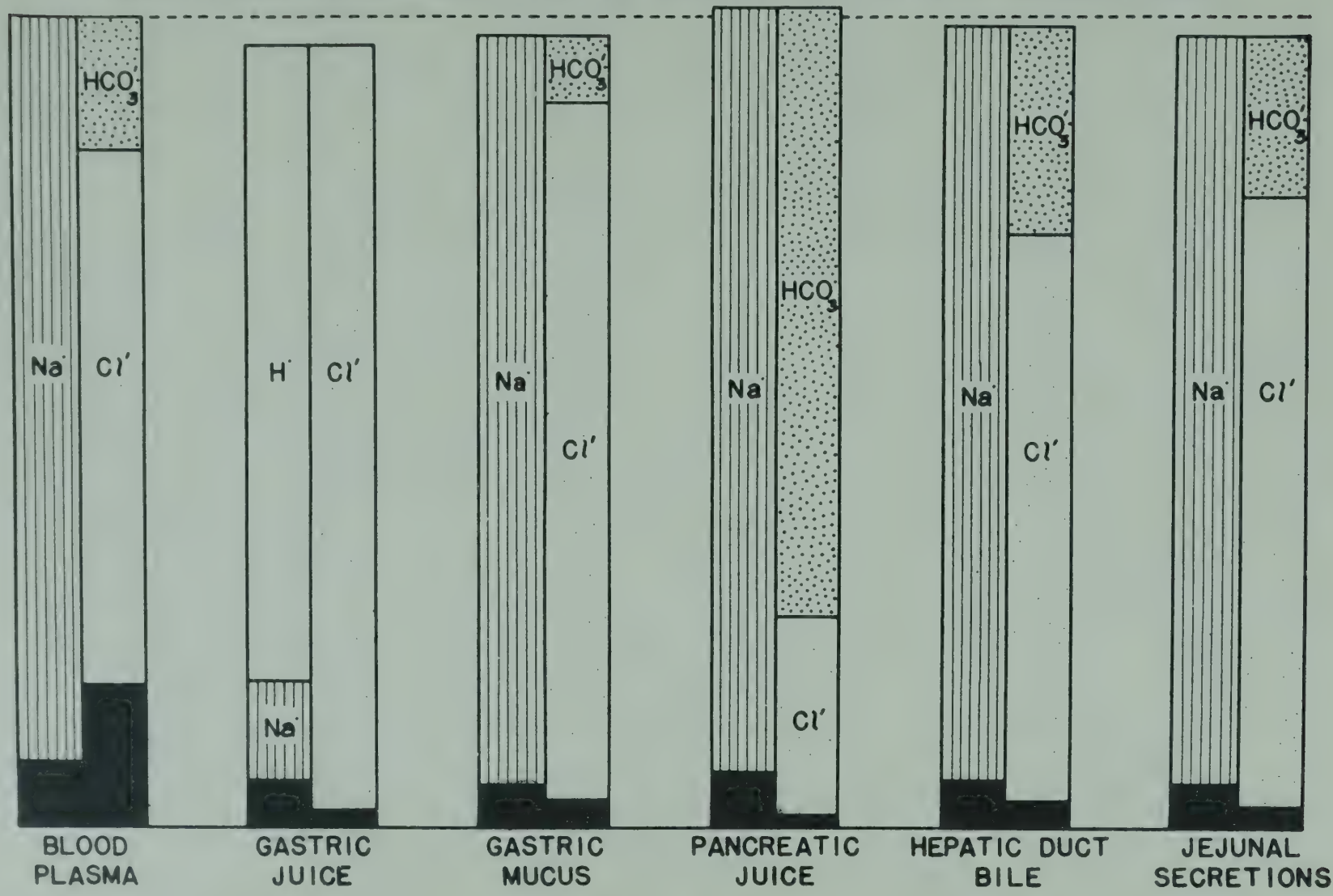


CHART 38

The data in this chart will serve to illustrate the rapidity of loss of extracellular water and electrolyte when reabsorption of gastric secretions is prevented. They were obtained from rabbits following obstruction of the pylorus by ligature. Rabbits do not vomit and secretions are not to an appreciable extent reabsorbed by the gastric mucosa. The stomach therefore collects and becomes enormously distended by the secretions entering it following obstruction of pylorus. The animals were sacrificed near the end of the survival period and the quantities of water, fixed base, and chloride ion found in the stomach were measured and are recorded in the table. The fixed base is almost entirely composed of sodium (Chart 38). Estimations of the quantities of water, fixed base, and chloride ion in the plasma before obstruction of the pylorus are also given in the table. As may be seen, the loss of fixed base is twice the initial plasma content and is accompanied by a somewhat larger loss of water. These measurements describe an extensive depletion of interstitial fluid in support of the blood plasma. The volume of interstitial fluid is about three times that of blood plasma (Chart 1). These data therefore indicate a removal of two-thirds or more of the interstitial reservoir. As regards the rapidity of this process of dehydration by loss of stomach secretions, it may be noted that the survival period of these animals was from 36 to 42 hours. These measurements make clear the dangerous situation of an infant suffering from diarrhoeal disease who is losing not only gastric but also duodenal and upper intestinal secretions.

The quantity of chloride ion found in the stomach is nearly four times the initial plasma content. This much more rapid loss of chloride ion than of fixed base causes the structural distortion shown in diagram 3, Chart 6. So that, in addition to the volume change (dehydration) caused by loss of water and fixed base, there is also reaction change (alkalosis).

LOSS OF WATER, FIXED BASE AND CHLORIDE ION IN GASTRIC SECRETIONS FOLLOWING PYLORIC OBSTRUCTION. (DATA FROM RABBITS.)

WATER LOST,	203 CC.	
INITIAL PLASMA VOLUME,	83 CC.	
FIXED BASE LOST,	270 CC.	0.1N
INITIAL PLASMA FIXED BASE,	140 CC.	0.1N
CHLORIDE ION LOST,	309 CC.	0.1N
INITIAL PLASMA CHLORIDE ION,	85 CC.	0.1N

AV. OF VALUES FOUND IN FOUR EXPERIMENTS

CHART 39-A

CHART 39-B

Reabsorption of water and electrolyte from the digestive secretions requires absorption by the intestinal tract of large additions to the quantities of water and of the extracellular electrolytes, sodium and chloride provided by intake. The extent of these additions is illustrated by the diagrams in the chart. The daily volume of the digestive secretions of a 7 Kg. infant is taken as one liter and food intake as one liter of a 3:1 dilution of cow's milk. The total volume of water presenting for absorption is thus about double the volume of intake. Owing to the much larger concentrations of sodium in the digestive secretions than in milk, absorption of sodium, if complete, is approximately seven times intake. Under normal circumstances these absorption assignments are accomplished with remarkable success and only the small remnants of water and sodium shown in the chart escape absorption and are lost in the stools. With the large increase in the volume of stools caused by diarrhoeal disease, the quantities of water and sodium escaping absorption are greatly extended. Owing to the relatively much larger requirement for absorption of sodium than of water shown by the diagrams, loss of sodium in the stools beyond the loss of water may be expected under the circumstance of hyperperistalsis. This is shown to occur by increase in the concentration of sodium in diarrhoeal stools along with the increase in volume. The chart serves to make clear the particularly hazardous position of the extracellular electrolytes in diarrhoeal disease.

CHART 39-C

The food intake of an infant provides water and the extracellular electrolytes, sodium and chloride, in large excess over obligatory expenditures. Owing to the ability of the kidney to extensively limit outgo in the urine, large losses in the stools can be covered, provided the usual food intake is sustained or even when considerably lowered. Diarrhoea, therefore, does not necessarily cause dehydration. The diagrams in the chart serve to illustrate these statements.

The usual values for the components of the water exchange for a 7 Kg. infant are shown in the first diagram. Water outgo in the stools is relatively small; the insensible expenditure has an approximately stationary value; and, except for the small daily retention of water required by growth, the large remainder from intake is removed in the urine. In the next diagram, water outgo in urine

DAILY ABSORPTION OF WATER AND SODIUM

7 KG. INFANT. INTAKE, 1000 CC. COW'S MILK AND WATER 3:1

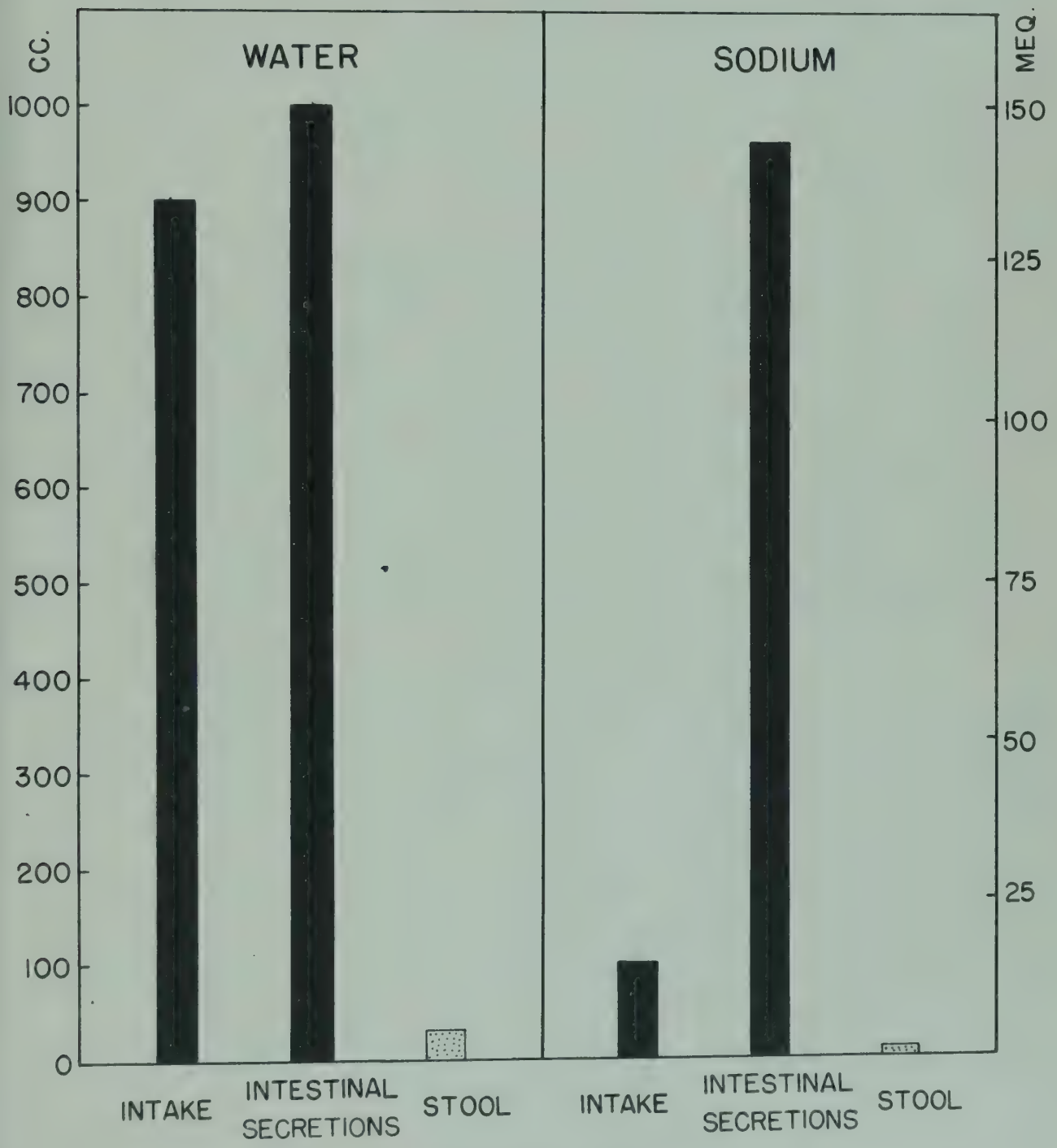


CHART 39-B

is reduced to the minimal quantity required by the kidney. The extent to which water can be lost in the stools in the presence of a usual intake without causing deficit is thus defined. According to the data of Holt, Courtney and Fales, the volume of stools in severe diarrhoea may be taken as 300 cc., with the reservation that there is often large increase beyond this value. As shown by the broken line across the diagram, the usual water intake can be reduced by about one-third in the presence of a water loss in the stools of 300 cc. without causing water deficit.

Sodium intake is enormously above the retention requirement for growth. Outgo in normal stools being relatively very small, the huge surplus from intake is removed in the urine. When there is need for conservation of sodium, outgo in the urine is reduced and can be brought down to the very small quantity defined by the limit of renal osmotic work capacity (Chart 17-F). The position of sodium balance in diarrhoeal disease is not, however, as secure as the diagram suggests. The loss of sodium in diarrhoeal stools is relatively larger than the loss of water (Chart 39-B). Taking the average value found for a stool volume of 300 cc., the permissible reduction of usual intake without causing sodium deficit is, as shown in the diagram, somewhat less than for water.

It is evident from the diagrams that, owing to the wide range of renal regulation of water and of sodium removal in urine, the large outgo in diarrhoeal stools will usually not cause deficits unless accompanied by reduction of food intake. Gastric intolerance for food is a widely variable feature of diarrhoeal disease. It may be complete with resulting rapid dehydration. In the chronic diarrhoeas tolerance for a usual or not greatly lowered food intake is often found and dehydration does not develop even when stools are very large. Requirement for parenteral provision of water and the extracellular electrolytes, sodium and chloride, in diarrhoeal disease depends largely on the extent to which food can be taken.

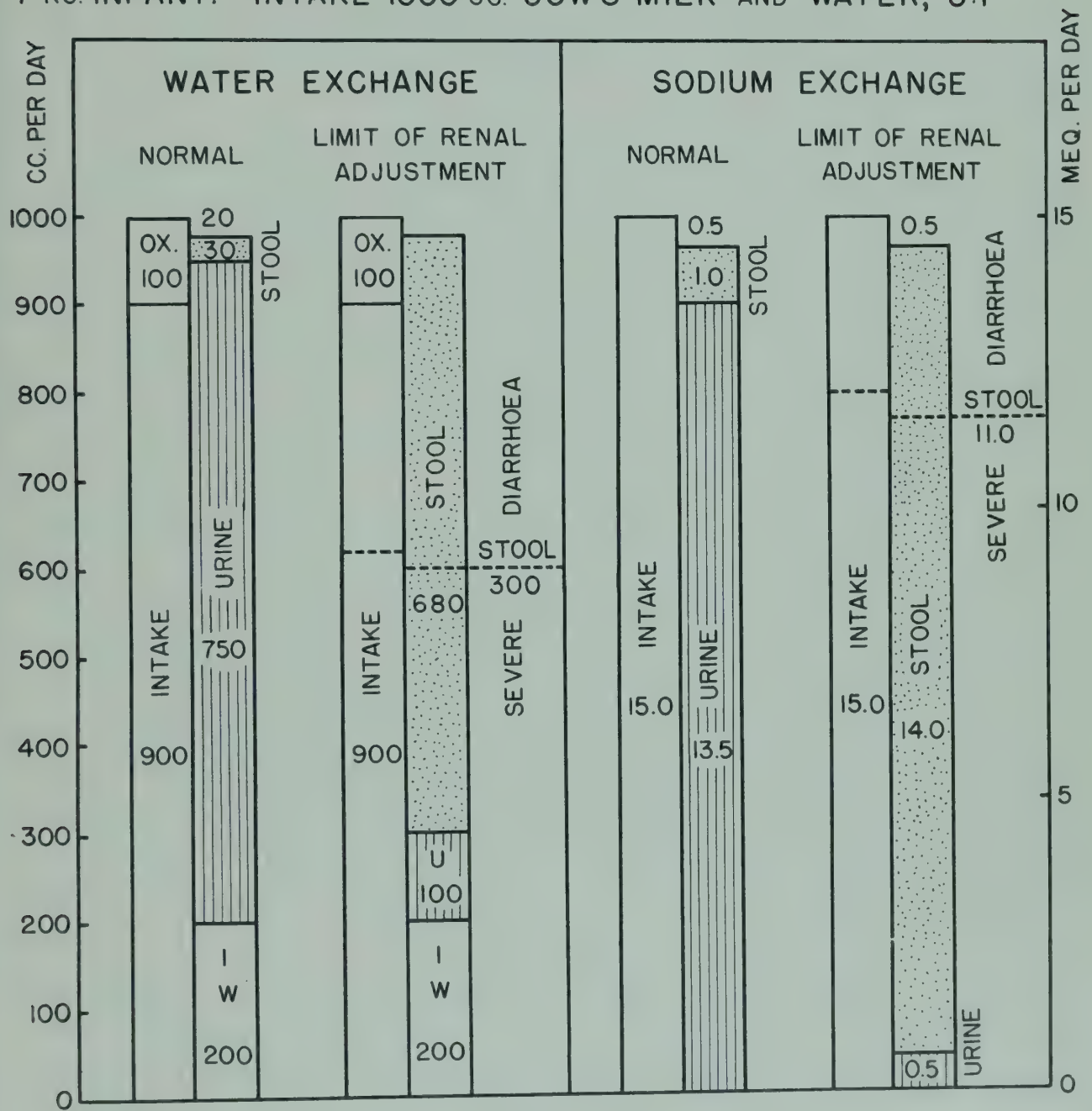

7 KG. INFANT. INTAKE 1000 CC. COW'S MILK AND WATER, 3:1
CC. PER DAY
MEQ. PER DAY
WATER EXCHANGE
SODIUM EXCHANGE
NORMAL
LIMIT OF RENAL ADJUSTMENT
NORMAL
LIMIT OF RENAL ADJUSTMENT
OX.
100
20
30
STOOL
INTAKE
900
URINE
750
I
W
200
OX.
100
STOOL
680
STOOL
300
DIARRHOEA
SEVERE
INTAKE
900
U
100
I
W
200
0.5
1.0
STOOL
INTAKE
15.0
URINE
13.5
0.5
DIARRHOEA
STOOL
11.0
SEVERE
INTAKE
15.0
STOOL
14.0
URINE
0.5
1000
900
800
700
600
500
400
300
200
100
0
15
10
5
0

CHART 39-C

When dehydration develops rapidly, the rate of transfer of interstitial fluid to the vascular compartment usually falls considerably short of replacement of plasma losses, and incomplete defense of plasma volume is shown by increase in the concentration of protein and in the volume of blood cells as measured by the hematocrit.

When, however, dehydration proceeds more gradually, defense of plasma volume may be completely successful over a prolonged period. This chart records the results of an experiment in which dehydration was produced by draining away the external secretion of the pancreas through a fistula. The animal, a dog, was fed minced and washed meat which provided almost no intake of sodium. Water intake was not restricted. Dehydration from continued loss of sodium in pancreatic juice is approximately measured by decline in body weight, which, it will be noted, begins at the outset of the experiment. The other curve in the chart is constructed from measurements of plasma protein concentration. According to plasma protein there is no change in plasma volume until the tenth day of the survival period. Then,over the several remaining days, protein concentration rises extensively, indicating rapid reduction of plasma volume. Other measurements showed an accurately sustained composition of the plasma over the 10-day period. Defects of the ionic structure then developed rapidly, and eventually there was severe acidosis. These data illustrate the excellence of plasma defense by the interstitial reservoir in the presence of moderately rapid dehydration. They also demonstrate that this defense reaches its limit abruptly. Clinically, they explain the symptomless early stages of progressive dehydration in diarrhoeal disease of infants followed by sudden development of the alarming manifestations of failure of the functions of the blood when the volume of the plasma can no longer be sustained.

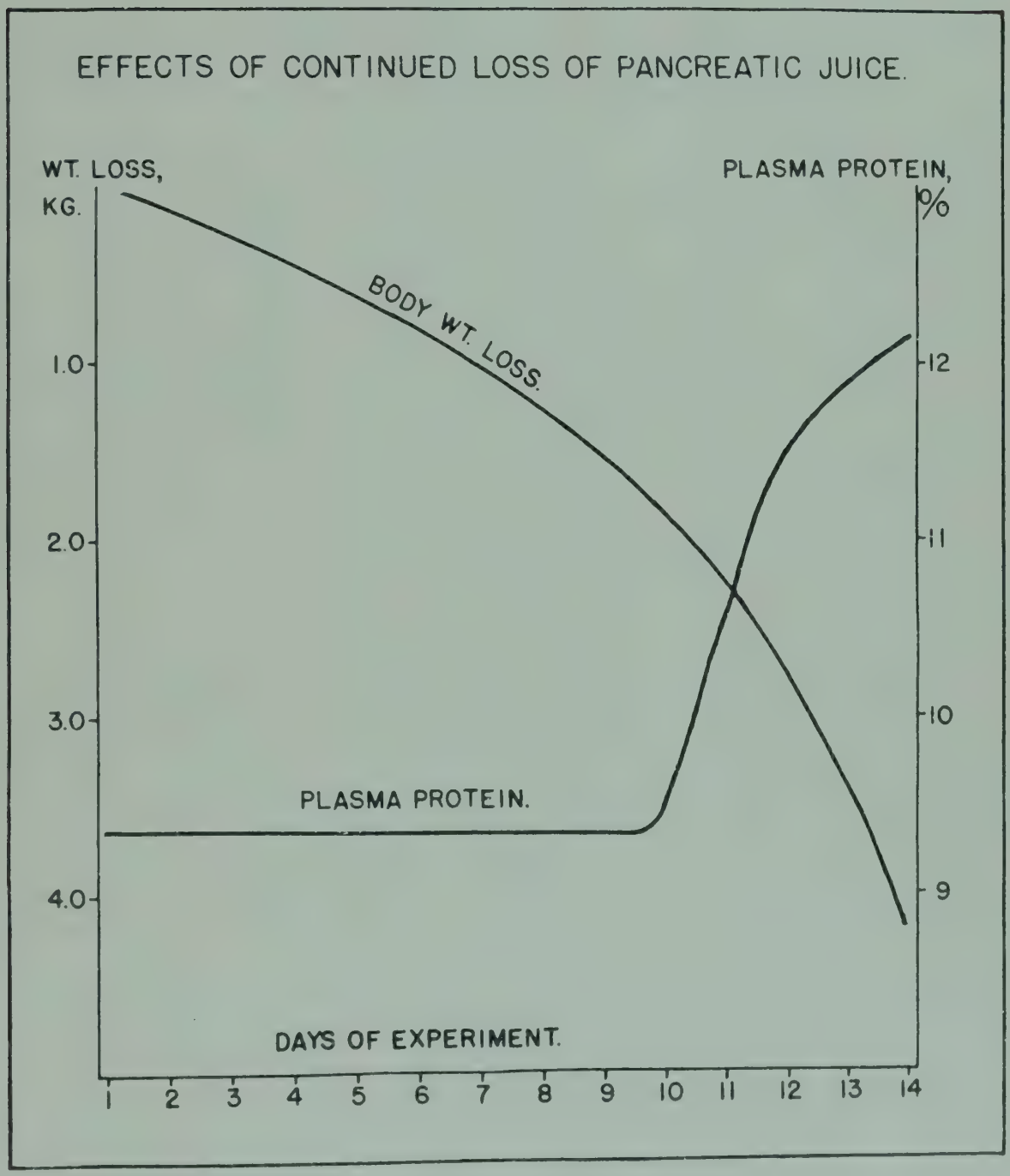

EFFECTS OF CONTINUED LOSS OF PANCREATIC JUICE.
WT. LOSS, KG.
PLASMA PROTEIN, %
BODY WT. LOSS.
PLASMA PROTEIN.
1.0
2.0
3.0
4.0
12
11
10
9
DAYS OF EXPERIMENT.
1 2 3 4 5 6 7 8 9 10 11 12 13 14

CHART 40-A

Processes of dehydration involve loss of intracellular as well as of extracellular fluid. This loss has two components. 1) The consumption of body protein, which results from partial or complete starvation incidental to most situations which produce dehydration, requires removal of water and solutes to an extent which will preserve the normal protein: cell volume relation (protein 1 gm.: water 3 gm.) and the normal concentrations of the other solutes. This water loss can be estimated from measurement of protein loss (nitrogen deficit x 6.25 x 3 = water loss). 2) In severe dehydration additional water withdrawal is found accompanying loss of the other cell fluid solutes beyond the loss of protein. In dehydration by thirsting this additional loss of cell fluid relates to distribution of water deficit between the extracellular and intracellular fluids (Chart 56). In diarrhoeal disease an apparently primary loss of intracellular electrolyte (requiring parallel loss of water) is found. Measurement of loss of the intracellular base potassium serves as a means of estimation of the overall loss of cell water on the premise of preservation of the normal potassium: water relation, K,1 millimol: water, 6 gm. (K,m-mol x 6 = Water loss, gm.).

The relatively larger loss of potassium than of protein in dehydration produced by thirsting and by diarrhoeal disease is shown in the chart by adjusting the ordinate scales to the normal protein: potassium ratio in cell fluid (protein, 2 gm.: potassium, 1 millimol). The equality of losses found for the adult receiving water abundantly and glucose indicate removal of intracellular fluid to the extent required by consumption of protein. Nearly equivalent losses are found for fasting but are larger because of absence of the protein sparing effect of glucose. Thirsting does not increase the loss of protein beyond the extent found for fasting but does greatly increase the loss of potassium, indicating additional withdrawal of intracellular fluid. The data from infants suffering from diarrhoeal disease and receiving glucose to limit consumption of body protein and salt solution to replace losses of extracellular fluid, display a large extension of potassium loss beyond the loss of protein. The data clearly suggest the desirability of replacement of this additional loss of potassium with expectation that provision of this large component of intracellular fluid fixed base will permit increase of cell fluid toward the volume prescribed by the normal protein: water relation. This is the premise of Darrow's recent introduction into parenteral fluid therapy of solutions containing potassium.

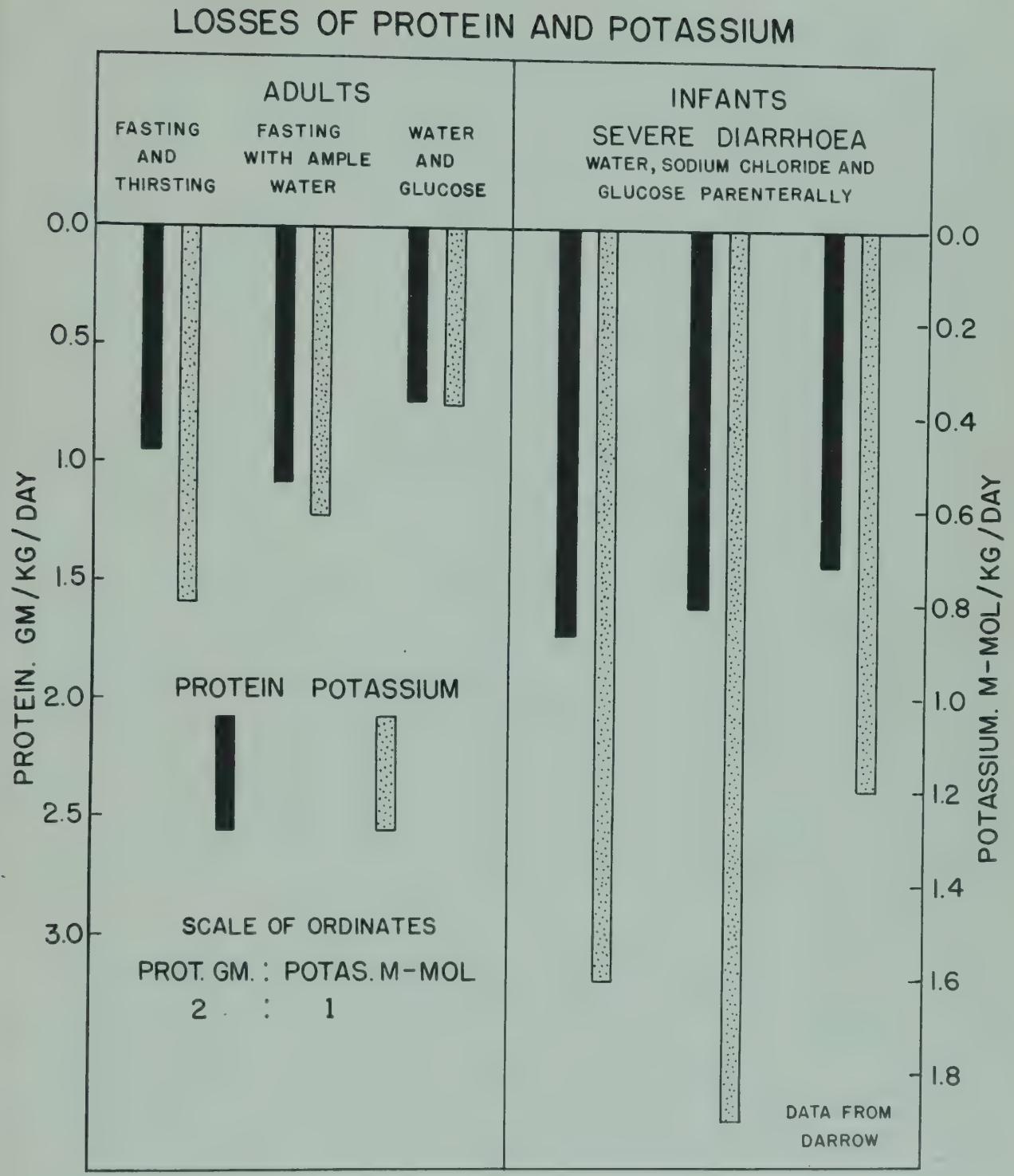

LOSSES OF PROTEIN AND POTASSIUM
ADULTS
FASTING AND THIRSTING
FASTING WITH AMPLE WATER
WATER AND GLUCOSE
INFANTS
SEVERE DIARRHOEA
WATER, SODIUM CHLORIDE AND GLUCOSE PARENTERALLY
PROTEIN GM/KG/DAY
POTASSIUM. M-MOL/KG/DAY
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
PROTEIN
POTASSIUM
SCALE OF ORDINATES
PROT. GM. : POTAS. M-MOL
2 : 1
DATA FROM DARROW

CHART 40-B

The most frequent cause of reaction disturbance is change in the concentration of bicarbonate from its normal value, decrease producing acidosis and increase alkalosis (metabolic acidosis or alkalosis, Chart 5-b, Section I). As shown in Chart 6, this change in bicarbonate is not a primary event. It is an adjustment, by the process of carbonic acid-bicarbonate buffering, to change in some other part, or parts, of the acid-base structure of extra-cellular fluid. Study of the pathogenesis of metabolic acidosis or alkalosis therefore consists in identification of the underlying structural change and explanation of its development in terms of accompanying abnormal circumstances. These are many and various. They may be considered conveniently under three headings:

I. Impairment of Renal Function. With the exception of protein, carbonic acid and bicarbonate ion, the normal values for the components of the electrolyte structure of extracellular fluid rest directly on renal control. It is therefore not surprising to find that disease of the kidney may permit the development of various defects. Another prominent cause of structural change in extracellular fluid is a secondary disturbance of renal function found in the advanced stage of dehydration. Eventual reduction of the volume of blood plasma by the process of dehydration causes physical changes in the blood, and in the mechanics of its circulation, which greatly reduce volume flow through the kidney with the result that accuracy of renal function is extensively impaired. In this group also may be placed the defect in renal control seen in Addison's disease which seems to be due to a failure of hormonal assistance.

II. Loss of Gastro-Intestinal Secretions. Many conditions of disease may disturb gastro-intestinal function to the extent of causing continued vomiting and diarrhoea and thus set up a process of withdrawal of water and electrolytes from extracellular fluid (Charts 37, 38, 39 and 40). Besides the changes in extracellular fluid directly caused by losses of its compo-

nent materials, the accompanying dehydration may eventually produce, as mentioned above, further defects of structure by disabling renal control.

III. Abnormal Acids in Extracellular Fluid. These are usually the ketone acids which appear in extracellular fluid whenever carbohydrate metabolism falls below the level required for the complete oxidation of fat. The ketone acids must be given place in the electrolyte structure while being carried to the kidney for removal in urine.

Identification of the plasma defect which has caused an observed change in bicarbonate theoretically requires a complete dissection of the electrolyte structure. Fortunately, however, a fairly satisfactory account of the bicarbonate change can be obtained from three measurements. The sum of the values of $Na^{\cdot}$, $K^{\cdot}$, Ca and $Mg^{\cdot\cdot}$ (total fixed base) can be measured in a single procedure. Change in this value can be referred almost dependably to its dominating component, sodium. Change in the relatively very small concentrations of the other three cations of a magnitude which would appreciably alter the concentration of bicarbonate ion is very unusual. The other two measurements required are of bicarbonate ion and chloride ion. If the sum of the values found is subtracted from the value for total base, a measurement of the combined base equivalence of $HPO_4^{\prime\prime}$, $SO_4^{\prime\prime}$, organic acids, and protein is obtained. The diagrams in this chart and in several which follow it are constructed from measurements of total base, bicarbonate ion, and chloride ion obtained from individual patients. Total base is designated B, and the remainder of the acid column, which contains the relatively small and individually unmeasured anion values, R.

The second diagram in the chart is constructed from measurements obtained from a patient suffering with the nephrotic type of renal disease and describes the changes in plasma structure which are fairly regularly found. These are a small reduction of base, a considerable extension of (Cl') and a relatively large reduction of (R). The decrease in(R) is referable to the low plasma protein which is characteristic of this disease. Increase in (Cl') is a rather unusual structural change in plasma. It is possible that here this change and the inverse change in base are referable, not to renal control, but to preservation of the normal osmotic value in the presence of decrease of plasma protein. If the loss of multivalent

protein were completely replaced by univalent ions, total ionic concentration would be above the normal value (Chart 2). The net result of these changes, as regards (HCO_3), is a moderate reduction.

In chronic nephritis, a large variety of plasma defects have been observed. The change which is perhaps most consistently present is an extension of (R). It has been found that this is composed of increased concentrations in the plasma of HPO_4'' and SO_4'', and probably of organic acid radicals. The increase in(R) as shown in the diagram produces an approximately equivalent reduction of (HCO_3') and explains the moderate degree of acidosis often found in the course of chronic nephritis. The measurements in the last diagram are from a patient in the terminal stage of chronic nephritis. The very small bicarbonate concentration, which represents an extremely severe acidosis, is seen to be caused by two structural changes, an enormous extension of (R) and a large reduction of base. These changes result from errors in renal control in opposite directions. Extension of (R) represents failure to restrict the concentrations of HPO_4'', SO_4'', and organic acid to their normal relatively very small values. Reduction of (B), on the other hand, describes inadequate support of the largest component of plasma structure, sodium. Renal disability conventionally connotes inadequate removal of materials from the plasma ("retention"). It should, however, not be surprising to find the inverse error in control, especially if it be recalled that plasma values are not established by a process of direct removal of surplus, but by reabsorption minus surplus from tubular fluid. The relatively enormous requirement for the reabsorption of sodium and its companion ion, chloride, is shown in Chart 17.

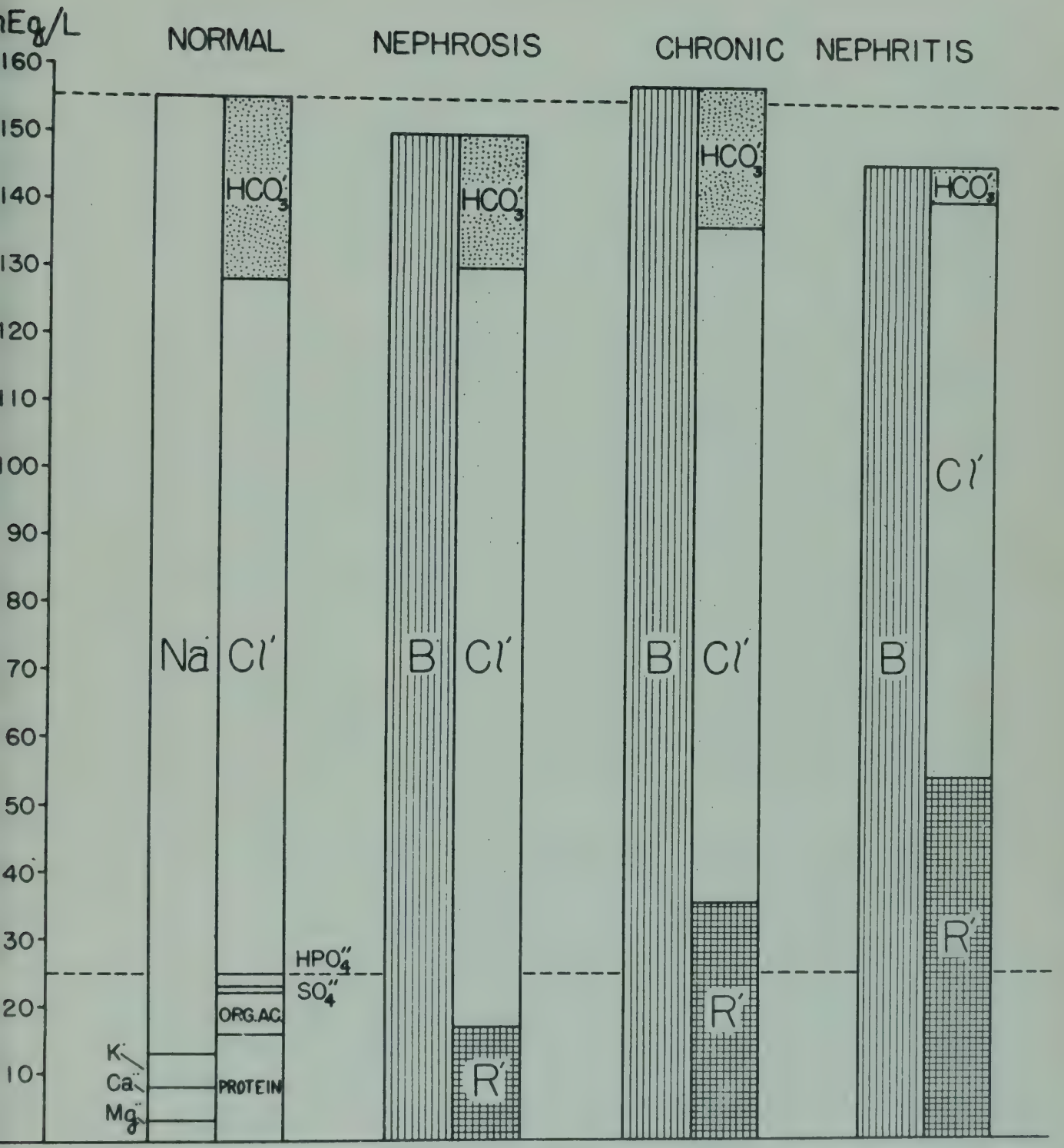

mEq/L
NORMAL
NEPHROSIS
CHRONIC NEPHRITIS
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
HCO'3
Na
Cl'
B
R'
HPO''4
SO''4
ORG.AC.
PROTEIN
K
Ca
Mg

CHART 41

The measurements from an infant who habitually vomited a large part of his feedings show a moderate extension of (HCO_3') produced by a corresponding recession of (Cl'). The reduction of chloride ion is referable to a small but continued wastage of gastric secretions. This loss of chloride ion is accompanied by a much smaller but appreciable loss of sodium (Chart 38). Owing to the close relationship of (B) to the osmotic value of the plasma (Chart 6), the water content of the plasma is adjusted by the kidney to the loss of sodium with the result that, as may be seen in the diagram, the normal value for (B) is sustained.

The diagram constructed from measurements from a patient with complete obstruction of the pylorus, shows as a result of protracted vomiting of stomach secretions a reduction of (Cl') to about one-third of its normal value. The compensatory extension of bicarbonate represents an extremely severe degree of alkalosis. Two other structural changes are recorded in the diagram, a considerable reduction of (B) and a large increase in (R). These two changes were seen in the preceding chart in the diagram describing plasma defects found in advanced nephritis. Their appearance in the plasma of the patient with pyloric obstruction indicates severe disability of renal control caused by advancement of the process of dehydration, by loss of stomach secretions, to the stage of reduction of the volume of the blood plasma and of volume flow through the kidney. In the early stages of dehydration plasma volume is well sustained (Chart 40) and, as seen in the preceding diagram, renal control of (B) and (R) is accurate.

In the diagram describing the plasma of an infant suffering from severe diarrhoeal disease, these changes are again seen and are here also referable to an advanced stage of dehydration caused by loss of digestive secretions. Since in duodenal and upper intestinal secretions there is rather more of sodium than of chloride ion (Chart 38), the recession of (Cl') produced by loss of gastric secretions is not seen, and acidosis is found instead of alkalosis, the bicarbonate reduction being referable to the two changes, decrease in (B) and increase in (R), indirectly caused by the process of dehydration.

It should be noted that the large extensions of (R), seen in the last two diagrams, are not entirely composed of increments of HPO_4'', SO_4'', and organic acids, as in chronic nephritis (preceding chart), but are also to a considerable extent referable to increase in the concentration of protein caused by reduction of plasma volume (Chart 40).

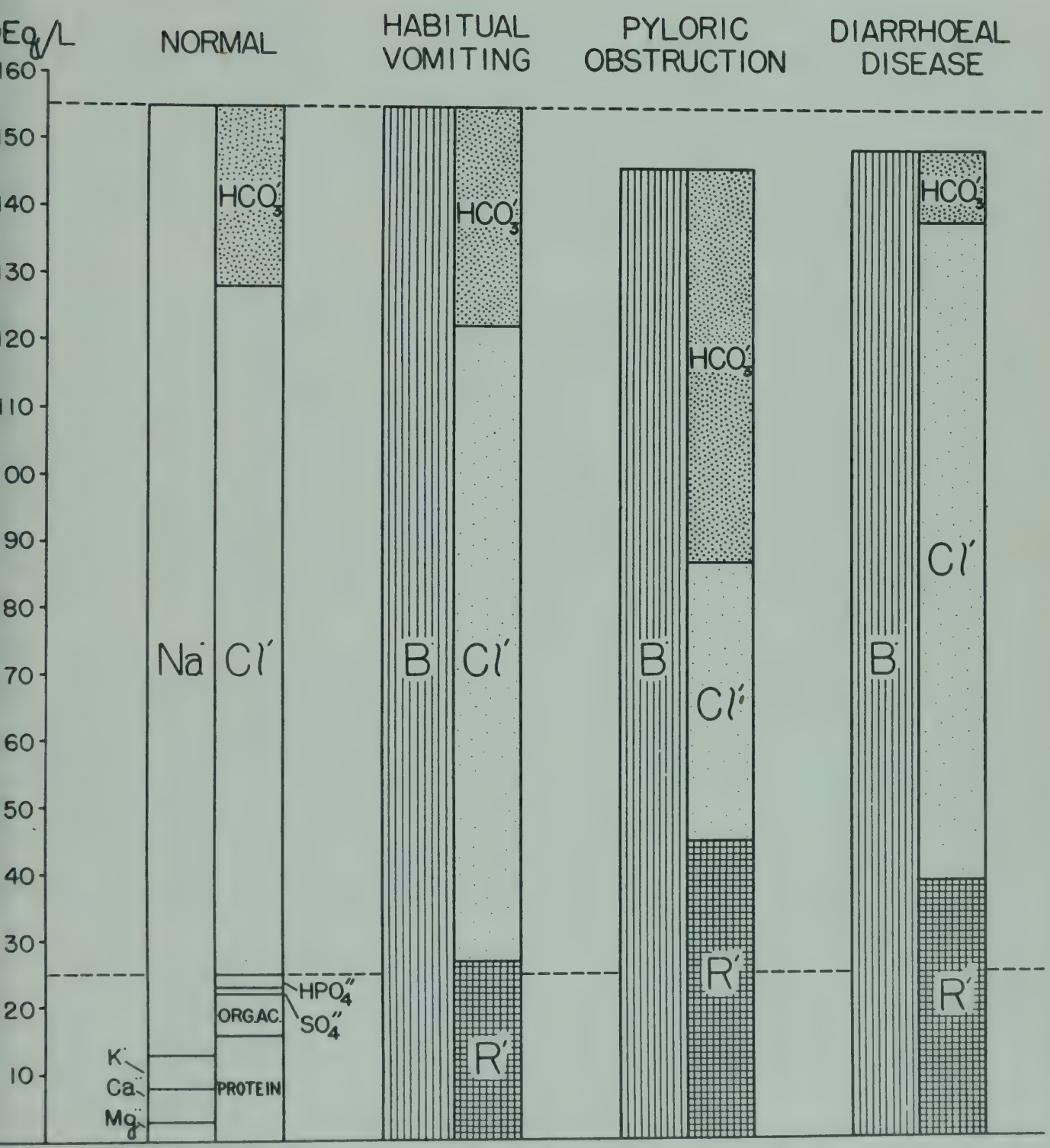

Eq/L
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
NORMAL
HABITUAL VOMITING
PYLORIC OBSTRUCTION
DIARRHOEAL DISEASE
HCO'3
Na
Cl'
B
R'
HPO"4
SO"4
ORGAC.
PROTEIN
K
Ca
Mg

CHART 42

In diabetes, ketosis results from a failure of the oxidative processes of carbohydrate metabolism. In many other conditions of disease, ketosis may result from a lack or inadequacy of carbohydrate intake. Complete or partial starvation is often an incident of disease processes. Children exhibit ketosis much more frequently than adults. Apparently, during childhood, even very short periods of carbohydrate deprivation may lower the level of carbohydrate metabolism to the point where incompletely oxidized fatty acids begin to appear in extracellular fluid.

These ketone acids must be given space in the electrolyte structure of the plasma and this space is provided at the expense of the concentration of bicarbonate ion. The measurements used in constructing the diagram which describes the ketosis of fasting were obtained from an epileptic boy who was fasted as a therapeutic measure. As may be seen, the only change in plasma structure is reduction of (HCO_3') to an extent corresponding to the base equivalence of the ketone acids. The next diagram shows the complete removal of the ketone acids, and return of (HCO_3') to its usual value, produced by providing, over a 12-hour period, a small intake of carbohydrate (50 gm. cane sugar).

The last diagram in the chart describes the extensive structural changes found in the plasma of a child in diabetic coma, which have together produced an extremely severe acidosis. Besides the very large accumulation of ketone acids, two other changes, decrease of base and increase in (R), have contributed to the reduction of (HCO_3') to a very dangerously small value. These two changes are referable to renal disability caused by the rapid dehydration which is always a prominent feature of the situation in diabetic coma.

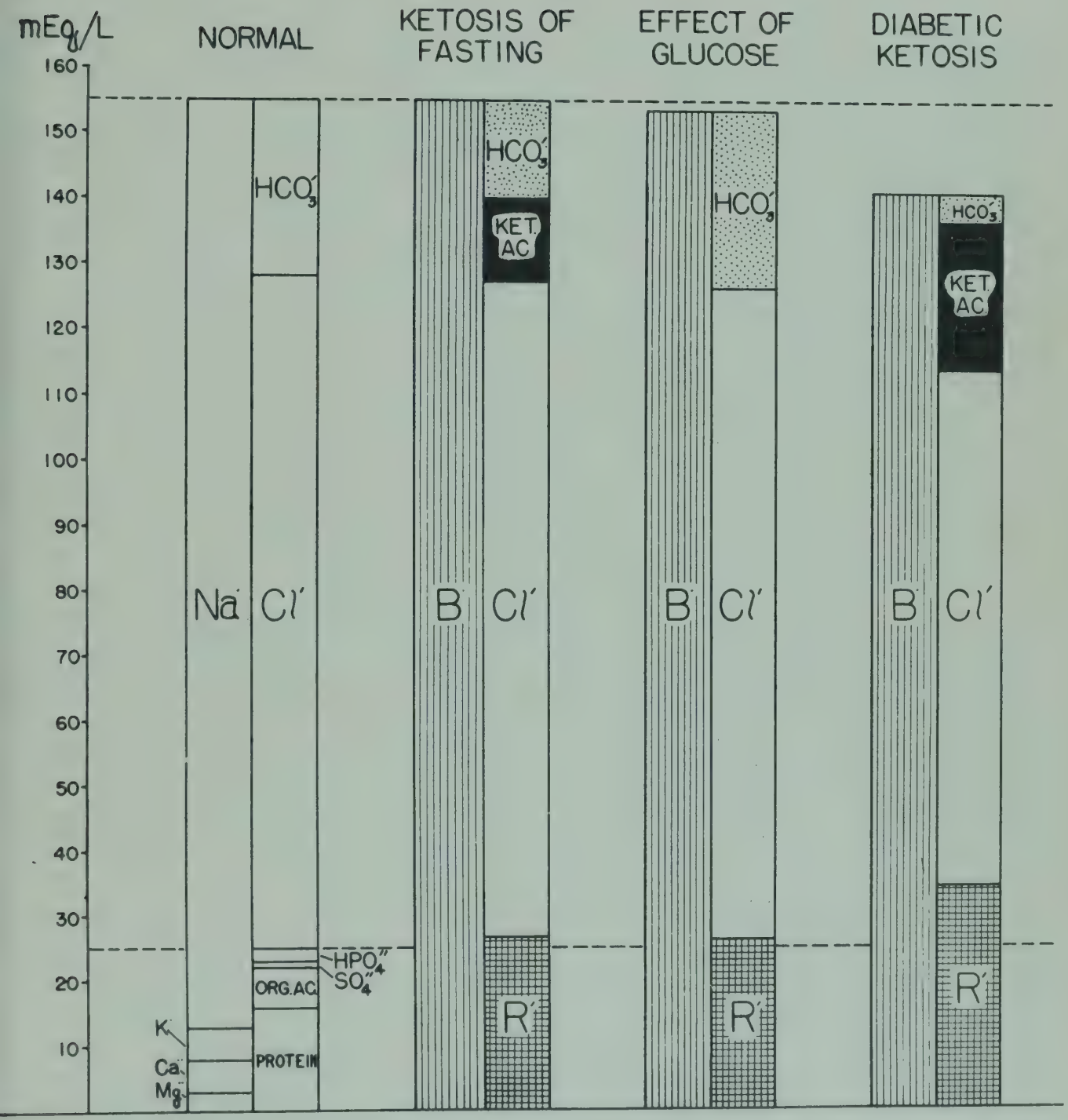

mEq/L
NORMAL
KETOSIS OF FASTING
EFFECT OF GLUCOSE
DIABETIC KETOSIS
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Na
Cl'
HCO3'
KET. AC.
B
R'
HPO4''
SO4''
ORG. AC.
PROTEIN
K
Ca
Mg

CHART 43

Since the space which the ketone acids occupy in the electrolyte structure of the plasma is always at the expense of bicarbonate, the inference is produced that ketosis regularly causes acidosis. This is usually, but not always, the case. The second diagram in this chart shows ketosis of severe degree in the presence of alkalosis. The measurements are from a child who was found to have an obstruction of the duodenum. The ketosis is referable to starvation incidental to the obstruction. The accumulation of ketone acids, although large, is not so large as the recession of chloride ion, caused by loss of stomach secretions by vomiting. Extension of bicarbonate is therefore necessary. Not infrequently, especially in children, ketosis develops, as illustrated here, in the presence of other processes of distortion of plasma structure. It is therefore evident that the presence of ketone acids in the urine does not dependably establish a diagnosis of acidosis.

The next diagram in the chart shows the change in plasma electrolyte structure which is characteristic of Addison's disease; a very large reduction of base (at the expense of sodium). This is accompanied by an equivalent recession of chloride ion which almost completely preserves bicarbonate. The moderate reduction of bicarbonate, according to the diagram, is referable to an increase in (R). The findings in Addison's disease indicate that renal support of the normal osmotic pressure of the plasma by integration of water and electrolyte removal is assisted in some way by the adrenal cortical hormone. In its absence there is wide discrepancy in the control of water and sodium. The almost determining relationship of the backbone of the electrolyte structure, sodium, to the osmotic value of the plasma has been considered (Charts 6 and 14).

The last diagram in the chart explains the reduction of plasma bicarbonate caused by ingestion of $CaCl_2$, one of the so-called acid-producing salts. As has been considered (Charts 29 and 30), these salts introduce chloride ion into extracellular fluid unaccompanied by the ingested base. The amounts of these salts given for therapeutic purposes are so large as to require a very considerable increase in the level of chloride ion transport in extracellular fluid. As may be seen in the chart, this extension of (Cl') causes an equivalent reduction of (HCO_3'). In the instance described by the diagram, the therapeutic use of $CaCl_2$ in a large dosage caused the reduction of the plasma bicarbonate to about one-third its usual value.

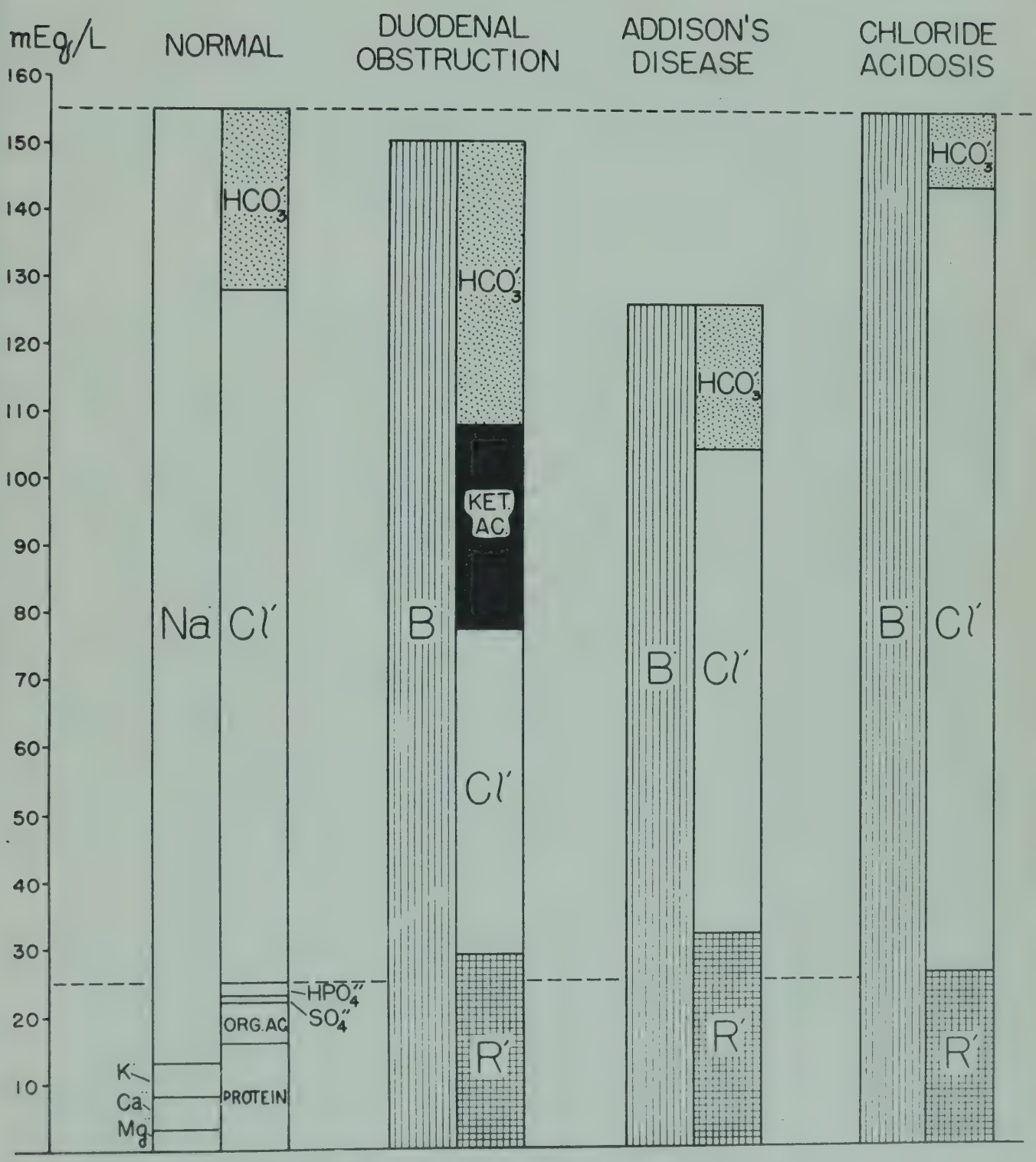

mEq/L
NORMAL
DUODENAL OBSTRUCTION
ADDISON'S DISEASE
CHLORIDE ACIDOSIS
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
HCO3
Na
Cl'
B
KET. AC.
R'
HPO4''
SO4''
ORG. AC.
PROTEIN
K
Ca
Mg

CHART 44

CHART 44 (Continued)

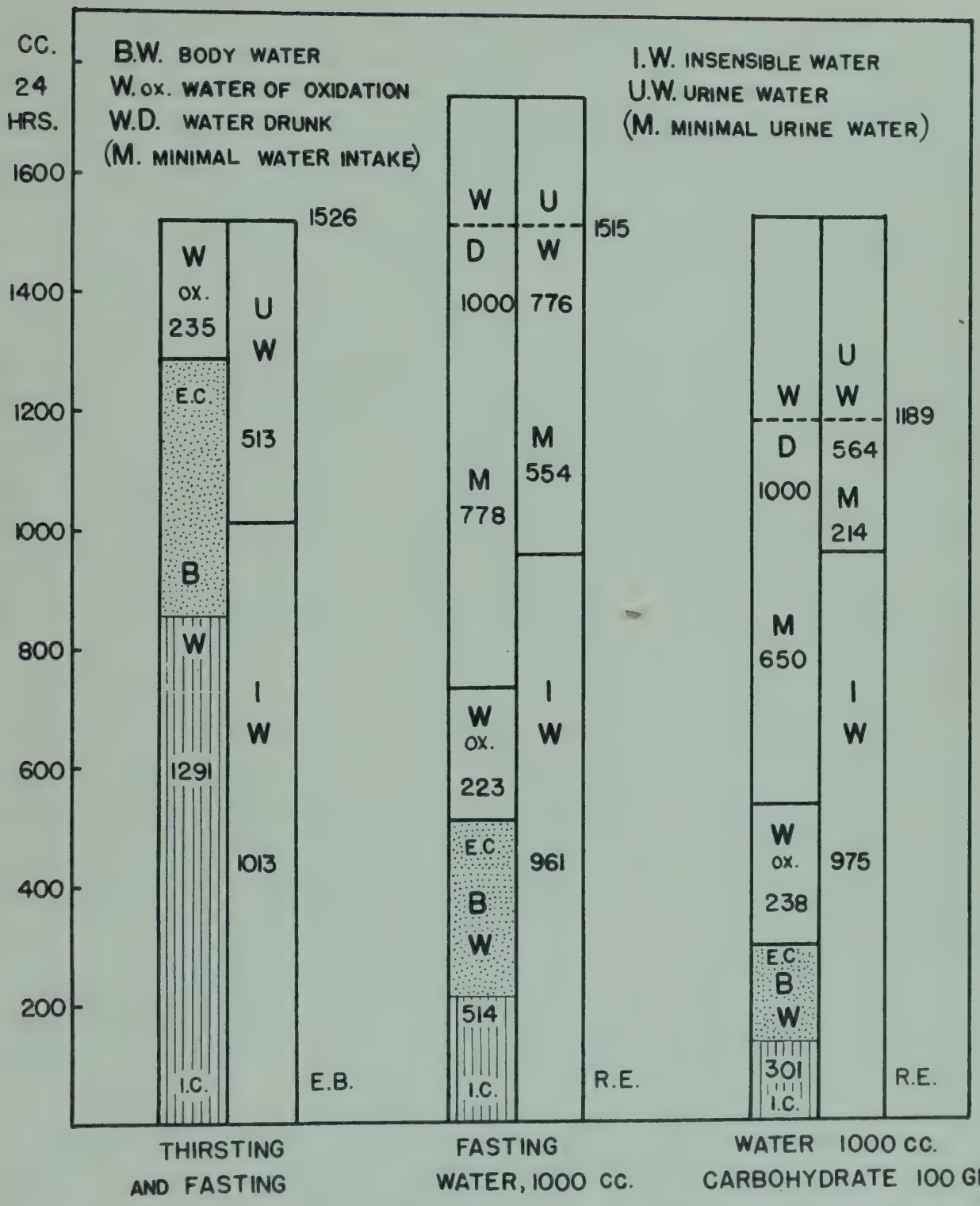
The diagrams in these last four charts, 41-44, describe various paths of pathogenesis of metabolic acidosis or alkalosis. Illustration of respiratory acidosis or alkalosis (Chart 5-b, Section II), in which an incorrect concentration of carbonic acid is the initial event and for which change in bicarbonate is compensatory, has been given in Chart 13. It should be remembered that, in this type of reaction disturbance, reduction of bicarbonate indicates alkalosis, and extension acidosis.

CHART 45

Abnormal circumstances which prevent an oral intake produce the requirement for parenteral administration of water. By giving glucose along with water, the water intake requirement is reduced and a larger conservation of body water is gained. These effects of glucose are shown in the chart. The diagrams record average values per day (omitting data from the first day) for the components of the water exchange found for a 4-day period of thirsting, a 6-day period of fasting with ample water intake and a 6-day period over which water and glucose were provided. The subjects were healthy young men.

As shown by the first diagram water expenditure in the absence of intake was approximately 1000 cc. by way of the lungs and skin (I.W.) and 500 cc. by the kidneys (U.W.). This obligatory outgo is covered to a small extent by water produced by oxidation of body fat and protein. The remainder is composed of preformed water (B.W.) withdrawn from the body. This water is taken from both the extracellular (E.C.) and intracellular (I.C.) body fluid compartments.

With ample water intake (second diagram) loss of body water is not prevented but there is extensive reduction; removal of water becomes proportional to the loss of body fluid solutes which is incidental to the state of fasting. Oxidation of protein requires removal of intracellular water and non-oxidizable solutes to an extent which will preserve the normal relationship of protein to cell volume. A loss of extracellular electrolytes also occurs during fasting and is accompanied by a parallel loss of water. The extent of body water loss (B.W.) during fasting and its partition as regards source is shown in the diagram. In order to determine the minimal water intake requirement it is necessary to define total obligatory expenditure. The larger component, I.W., because of its



COMPONENTS OF THE WATER EXCHANGE

CHART 45

relation to the energy metabolism has an approximately fixed value for a subject at rest. The minimal quantity of water required by the kidney can be derived from a measurement of total solute output, taking 1.4 osmolar as maximal for solute concentration in urine (Chart 17-B). The value found (M) completes definition of obligatory outgo (broken line). By carrying this line across the diagram the minimal water intake (M) is defined. Measured in this way the minimal requirement for fasting subjects has been found to be approximately 800 cc. per day.

The effects of an intake of carbohydrate on the components of the water exchange are shown by the third diagram. When 100 gm. of glucose are provided, there is a large reduction of the renal water requirement and a less extensive reduction of the preformed body water available for expenditure. This results in a reduction of the minimal water intake requirement to an extent which is approximately equivalent to the weight of glucose given; so that the intake requirement when glucose is given may be taken as 700 cc. instead of 800 cc. for the state of fasting. The data in the next two charts explain these effects and define the quantity of glucose required to gain them.

CHART 46

The renal water requirement rests directly on the total quantity of substances claiming removal in the urine. In the first section of this chart daily measurements of total urine solutes over a period of fasting and over other periods during which glucose was provided at several levels of intake are recorded. The data describe extensive reduction when glucose is given and show that this effect is approximately maximal for an intake of 100 gm. and amounts to more than one-half of the solute outgo found for fasting. The average daily values for the periods, omitting the first day, were

Fasting,	806	milliosmols
Glucose, 100 gm.,	342	"
Reduction	464	"

A considerable part of this reduction can be accounted for by the antiketogenic effect of glucose. In the second section of the chart the ketosis of fasting is measured by the increase of organic acids in the urine above the value found on the first day.

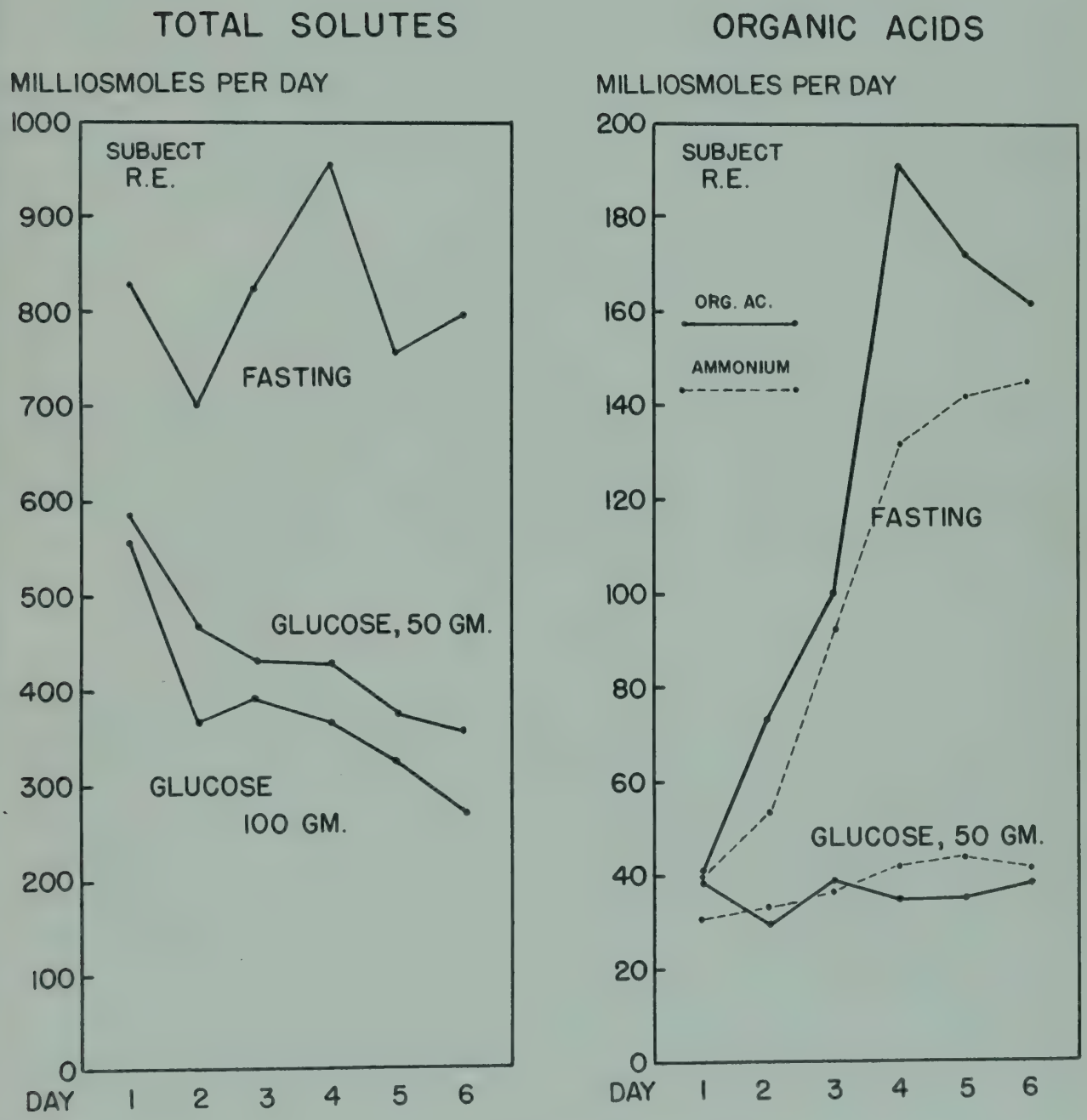

TOTAL SOLUTES
MILLIOSMOLES PER DAY
1000
900
800
700
600
500
400
300
200
100
0
SUBJECT
R.E.
FASTING
GLUCOSE, 50 GM.
GLUCOSE
100 GM.
DAY 1 2 3 4 5 6
ORGANIC ACIDS
MILLIOSMOLES PER DAY
200
180
160
140
120
100
80
60
40
20
0
SUBJECT
R.E.
ORG. AC.
AMMONIUM
FASTING
GLUCOSE, 50 GM.
DAY 1 2 3 4 5 6

CHART 46

There is no ketosis on the first day. Then, with consumption of the body's slender store of glycogen, there is progressive increase of the organic acid excretion which is composed of the ketone acids and reaches a maximum on the fourth day. This addition to acid excretion requires the increased production of ammonium recorded in the chart. Since 2 millimols of ammonium derive from 1 millimol of urea, the increase in urine ammonium adds to solute output to the extent of one-half of its equivalence. Taking the average of the increments of organic acids and ammonium above the values found on the first day, the addition to solute output composed of solutes produced by ketosis was:

Organic acid increment,	138	millimols
1/2 Ammonium " ,	57	"
	195	"

As shown by the data from the glucose period, an intake of 50 gm. daily prevents these increments. Reduction of the total solute output found for fasting when glucose is given amounts to 464 millimols (above). Prevention of ketosis accounts for 195/464 = 42% of the reduction of solute outgo gained by providing an intake of 100 gm. of glucose.

CHART 47

This chart describes the protein sparing effect of carbohydrate. The lowermost curve records the progressive consumption of body protein across a 6-day period of fasting. As shown by the other data, an intake of glucose reduces protein loss and the maximum of this effect is almost gained by providing 100 gm. daily and amounts to reduction of oxidation of protein to nearly one-half the extent found for fasting. This limit to protein sparing by glucose might be expected. The average daily consumption of protein over the period of fasting was 70 gm. When 100 gm. glucose was given protein loss was reduced to 40 gm. The minimal protein intake which will sustain nitrogen balance under normal circumstances has been found to be about 40 gm. daily. An intake of 100 gm. glucose approximately restores the physiological minimal level of protein metabolism.

The release of intracellular water incidental to the oxidation of body protein (3 gm. H_2O per gm. Protein) is recorded by the other ordinate of the chart.

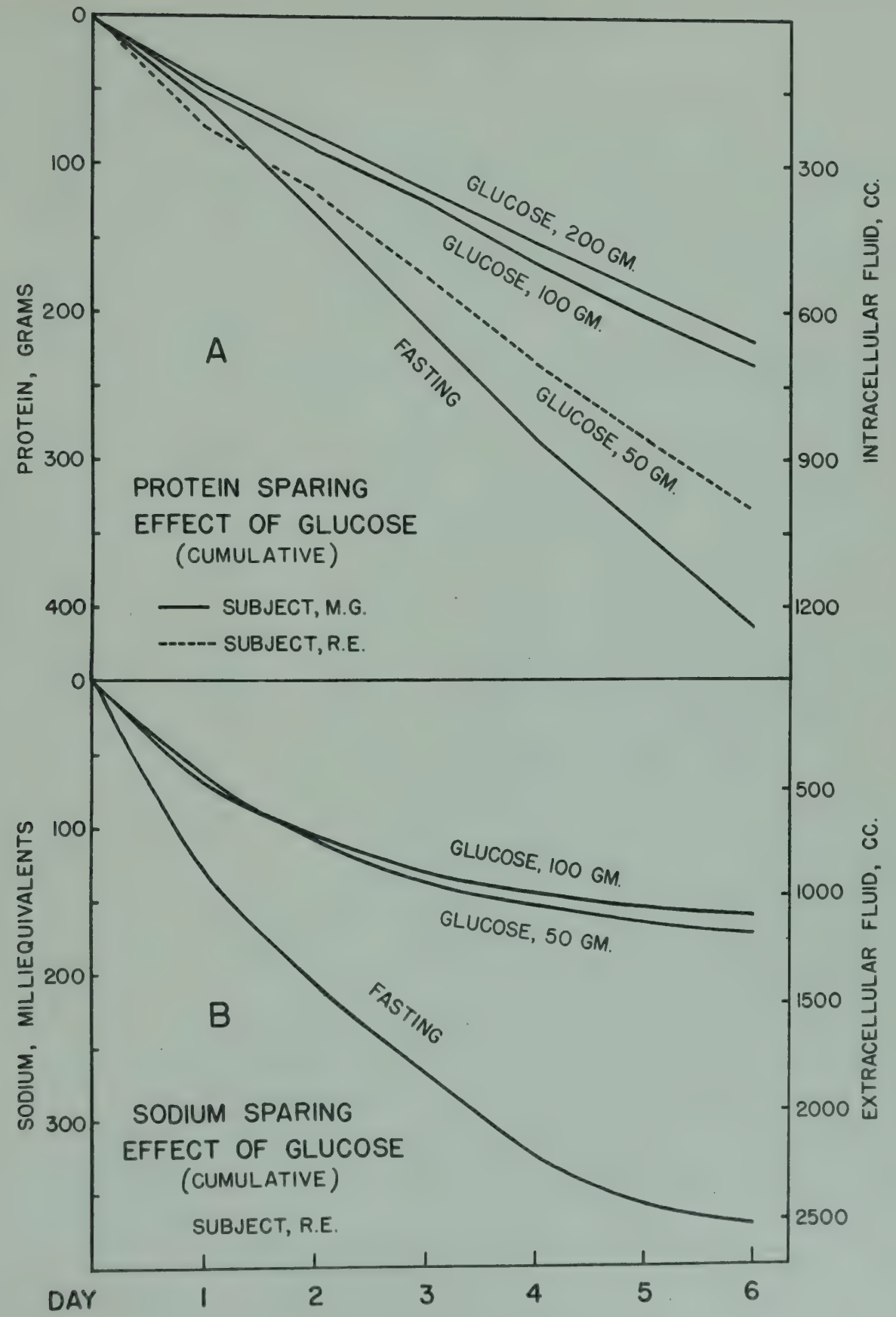

PROTEIN, GRAMS
INTRACELLULAR FLUID, CC.
0
100
200
300
400
300
600
900
1200
A
GLUCOSE, 200 GM.
GLUCOSE, 100 GM.
FASTING
GLUCOSE, 50 GM.
PROTEIN SPARING
EFFECT OF GLUCOSE
(CUMULATIVE)
SUBJECT, M.G.
SUBJECT, R.E.
SODIUM, MILLIEQUIVALENTS
EXTRACELLULAR FLUID, CC.
0
100
200
300
500
1000
1500
2000
2500
B
GLUCOSE, 100 GM.
GLUCOSE, 50 GM.
FASTING
SODIUM SPARING
EFFECT OF GLUCOSE
(CUMULATIVE)
SUBJECT, R.E.
DAY
1
2
3
4
5
6

CHART 47

The extent of reduction of solute output gained by the protein sparing effect of glucose may be roughly estimated from measurements of urine nitrogen expressed as millimols of urea. Average daily values (omitting the first day) were:

Fasting,	Urea 402	millimols
Glucose, 100 gm.,	252	"
Reduction	150	"

Reduction of total solute output was 464 m-osM (Chart 46). The sparing of protein by glucose thus accounts for 150/464 = 32% of this reduction.

Incidental to the sparing of protein and of water shown in the chart there is corresponding conservation of the non-oxidizable solutes of intracellular fluid. Urine potassium, for instance, was 50% less than was found for the fasting period.

There is also extensive reduction of the loss of extracellular electrolytes. As shown in the chart (B) which records losses of sodium during fasting and over other periods with differing intakes of glucose, the maximum of this effect is approximately gained by an intake of 50 gm. glucose daily and amounts to reduction of sodium loss to less than one-half the extent found for fasting with corresponding conservation of extracellular water.

CHART 48

Explanation of the sodium sparing effect of glucose shown in the preceding chart is not at hand. The large addition to the acid excretion composed of the ketone acids which develops in the state of fasting suggests requirement for an increased expenditure of fixed base, which is removed when ketosis is prevented by giving glucose. Body fluid base is, however, defended in the presence of acid excess claiming removal in urine by a regulated increase in the titratable acidity of the urine and of ammonium production (Chart 22). The accuracy of this defense of fixed base is shown in the chart. Ketosis is measured by recording additively the daily increments of total organic acids in urine above the value found on the first day of a 6-day fast. The increments of titratable acidity and of urine ammonia are also recorded. Taken together they closely cover the increased excretion of organic acids. These data make it clear that the ketosis of fasting does not require an increased

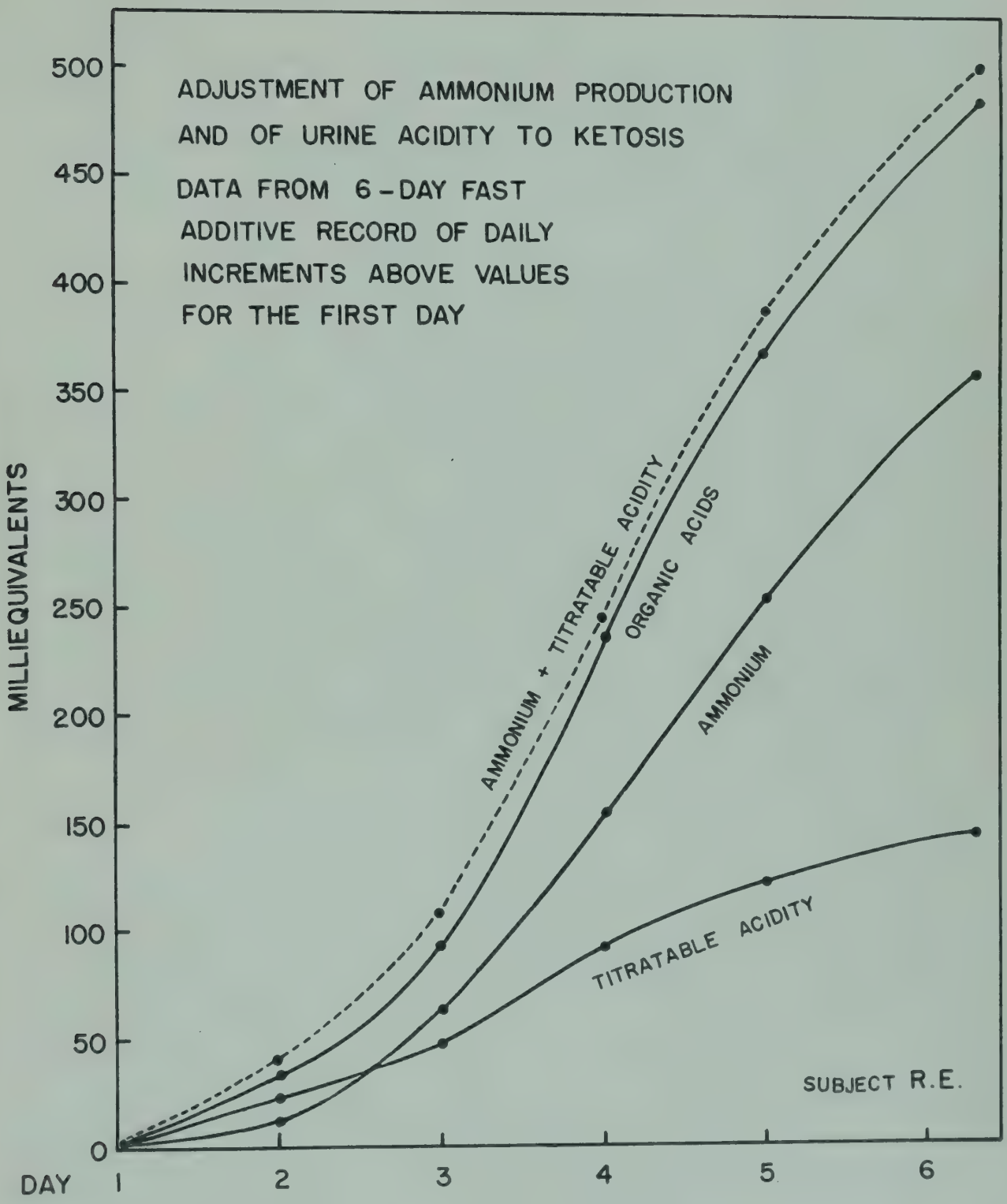

ADJUSTMENT OF AMMONIUM PRODUCTION
AND OF URINE ACIDITY TO KETOSIS
DATA FROM 6-DAY FAST
ADDITIVE RECORD OF DAILY
INCREMENTS ABOVE VALUES
FOR THE FIRST DAY
MILLIEQUIVALENTS
500
450
400
350
300
250
200
150
100
50
0
DAY
1
2
3
4
5
6
AMMONIUM + TITRATABLE ACIDITY
ORGANIC ACIDS
AMMONIUM
TITRATABLE ACIDITY
SUBJECT R.E.

CHART 48

excretion of fixed base and therefore does not explain the larger removal of sodium than is found when glucose is provided.

The sodium sparing effect of glucose, whatever its mechanism, provides valuable physiological benefit by reducing the loss of extracellular fluid to one-half the extent found in the state of fasting.

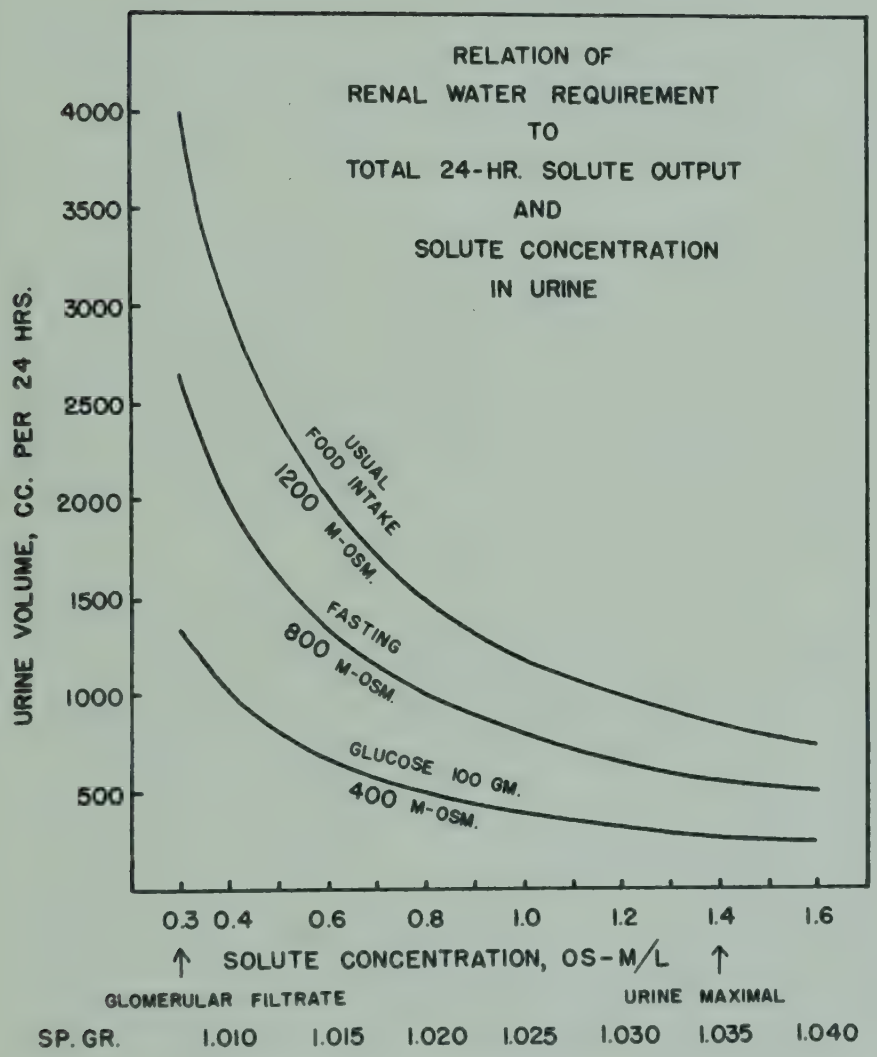
Summary of effects of glucose on the water exchange.

Reduction of the losses of the normal body fluid solutes below the values found for fasting is accompanied by an approximately parallel conservation of body water. There is, therefore, along with reduction of the renal water requirement a reduction of body water available for expenditure. As shown by the third diagram in Chart 45, the lowering of the renal water requirement when glucose is given is larger than the reduction of available body water. This can be explained by the absence of abnormal solutes, the ketone acids, which in the fasting state require for their removal about one-third of the minimal renal water expenditure. The more extensive reduction of the renal requirement than of available body water which produces corresponding lowering of the intake requirement is thus explained by the anti-ketogenic effect of glucose.

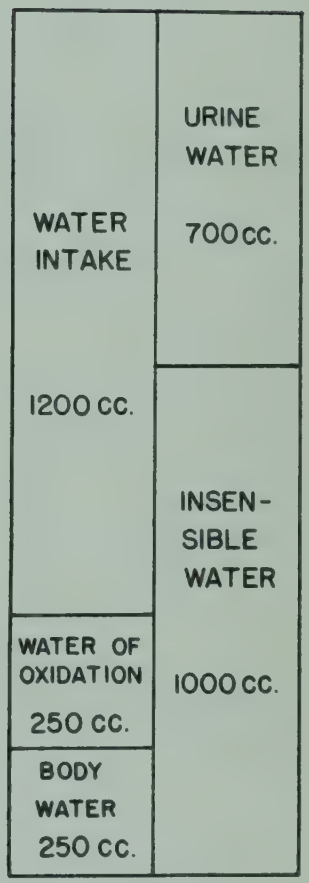
CHART 49

In parenteral fluid therapy glucose solution is used to cover the current obligatory expenditures of water by the body. As shown by the three preceding charts, glucose by itself provides several important physiological services, which for an adult, are gained from an intake of 100 gm. daily. The minimal water intake requirement for a subject receiving 100 gm. of glucose may be taken as 700 cc. daily, provided the kidney conserves water to maximal extent by secreting urine at an osmolar concentration of 1.4 (Chart 45). In clinical situations requiring provision of water parenterally, it is not necessary to demand of the kidney the osmotic work which maximal solute concentration in urine requires. Water can easily be provided to an extent which will permit the kidney to remove the solute load at a usual concentration. This may be taken as 0.6 osmolar which, for a usual assortment of solutes, corresponds to a specific gravity of 1.015.

A



B



WATER BALANCE
WITH GLUCOSE INTAKE
OF 100 GM. DAILY

CHART 49

CHART 49 (Continued)

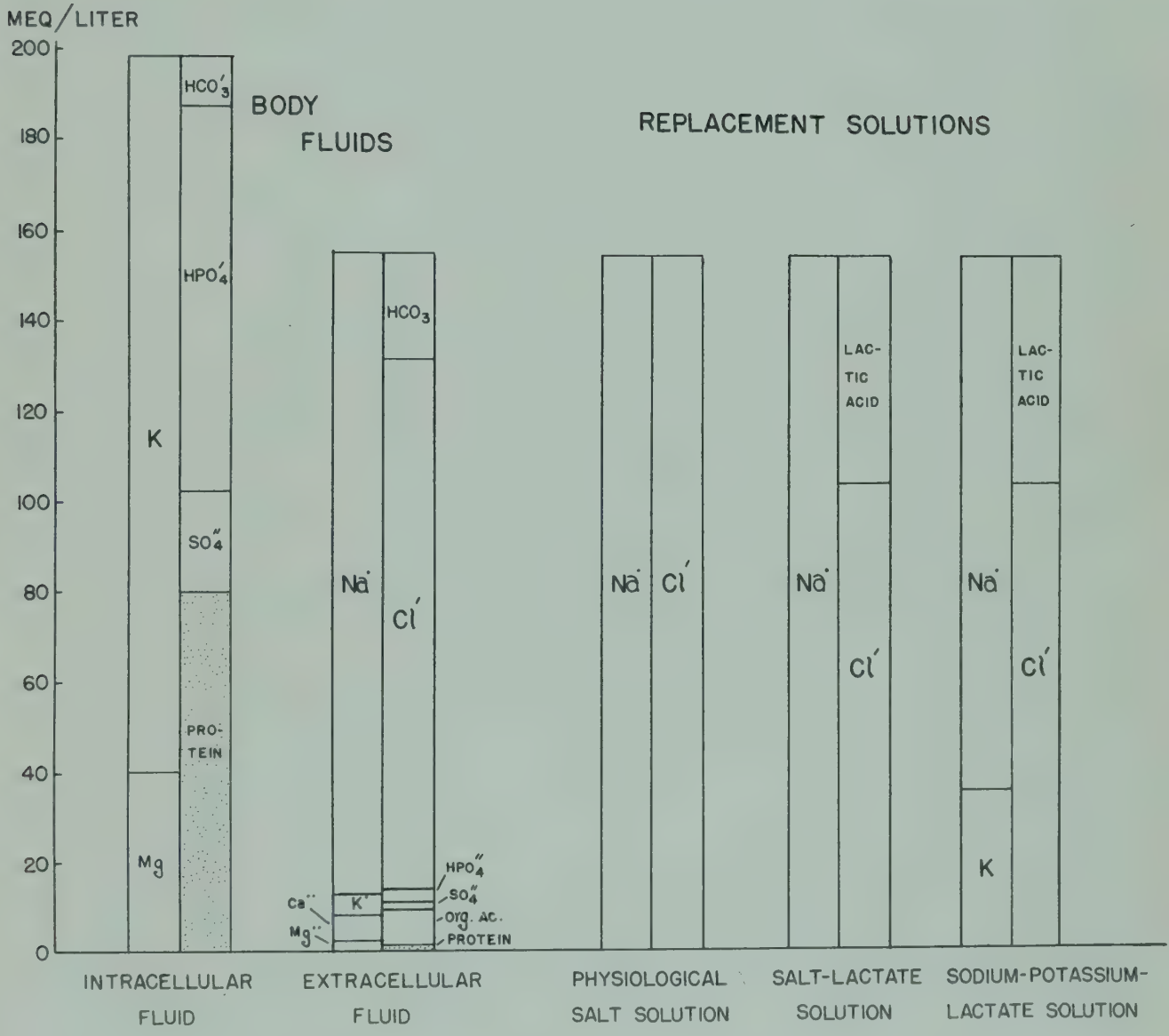
The chart (A) records the renal water requirements for removal of the solute load found for an ordinary food intake, for the state of fasting, and when an intake of 100 gm. of glucose is provided, over the range of urine solute concentration. Total solute output by a subject receiving 100 gm. of glucose is one-half of the output found for fasting (Chart 46) and one-third of the output which derives from a usual food intake. The renal water requirement in relation to urine solute concentration is correspondingly less; at maximal concentration, 1.4 osmolar, it is, according to the chart, 300 cc., and at a usual concentration, 0.6 osmolar, it becomes approximately 700 cc.

A liberal allowance for insensible water loss by a subject at rest is 1000 cc. Total daily expenditure is thus defined as 1700 cc. As shown in the chart (B) a portion of this outgo is covered by water produced by oxidation of body protein and fat and the glucose provided, and by the release of preformed body water beyond the sparing effects of glucose. The quantity of water within the body available for expenditure is taken as 500 cc. The diagram thus defines 1200 cc. as the water intake requirement.

According to these data the physiological requirement for water and glucose in parenteral fluid therapy will be met by providing 1200 cc. of an 8.5% solution of glucose. To give the requirement more convenient dimensions; 1-1/2 liters of 10% glucose solution should cover it abundantly.

CHART 50

The preceding chart presents approximate definition of the physiological requirement in parenteral fluid therapy; i.e. the requirement for water to cover obligatory expenditures and for glucose to provide to maximal extent its several services to body fluid physiology. Solutions of electrolytes are used parenterally to cover pathological processes of body fluid loss and to replace antecedent deficits. It is, then, expected that water provided as glucose solution will be spent but it is desired that water given with electrolytes be retained. This will not be the case unless the physiological requirement is completely covered by glucose solution. It is also to be noted that the physiological requirement remains stationary until oral intake is resumed whereas the requirement for water and electrolytes will decline as processes of dehydration abate and initial deficits are repaired. Neglect of this consideration leads to overhydration (Chart 35-B).


MEQ/LITER
200
180
160
140
120
100
80
60
40
20
0
BODY FLUIDS
REPLACEMENT SOLUTIONS
K
Mg
HCO'3
HPO'4
SO''4
PRO-TEIN
Na'
Cl'
HCO3
Ca''
K'
Mg''
HPO''4
SO''4
Org. Ac.
PROTEIN
LAC-TIC ACID
INTRACELLULAR FLUID
EXTRACELLULAR FLUID
PHYSIOLOGICAL SALT SOLUTION
SALT-LACTATE SOLUTION
SODIUM-POTASSIUM-LACTATE SOLUTION

In situations of extracellular fluid disturbance of such severity as to require energetic parenteral therapy, there is nearly always requirement for restoration of volume and repair of a large variety of structural deficits, illustrated by Charts 41-44. The accuracy of repair of structure from materials supplied rests on the kidney. As has been considered, there is, in advanced dehydration, extensive impairment of renal function. Restoration of renal control over the individual parts of the plasma structure is therefore immediately important and is gained from the water for renal expenditure which glucose solution provides. Structural distortion caused by space required for transport of ketone acids is directly repaired by glucose (Chart 43).

The replacement solutions in current use are shown in the chart. Only the two large components of extracellular fluid, Na and Cl, are supplied. As shown by the body fluid diagrams, the other components are present in intracellular fluid at very much larger concentrations. It is assumed that consumption of body protein beyond the protein sparing effect of glucose will release these materials to an extent which will abundantly sustain their relatively very small concentrations in extracellular fluid. It is, then, expected that the kidney, using the Na and Cl provided and the materials released from cell fluid, will rebuild the normal electrolyte structure in a restored volume of extracellular fluid. It is evident from the salt solution and extracellular fluid diagrams that restoration of one of the large components, bicarbonate ion ($-HCO_3$), will require removal of a large part of the chloride ion (Cl) supplied. The salt-lactate solution was designed by Hartmann to obviate this renal task. The lactic acid radical of sodium lactate is oxidized within the body and provides place for bicarbonate ion taken from carbonic acid (Chart 6). This solution is especially suitable when bicarbonate is below its usual value. It obviously should not be used when chloride recession has caused extension of bicarbonate (Chart 42); the lowered chloride will be raised more rapidly by salt solution. The sodium-potassium-lactate solution has been recently introduced by Darrow with the purpose of extending replenishment to intracellular fluid. As shown by the diagram the concentration of K is 8 times the normal value for extracellular fluid. A rise of plasma (K) to double its normal value carries the hazard of embarrassment of cardiac function. Darrow has thoroughly shown that this solution can be safely used provided infusion is gradual and follows initial restoration of renal function gained by glucose solution. This solution is an important addition to the

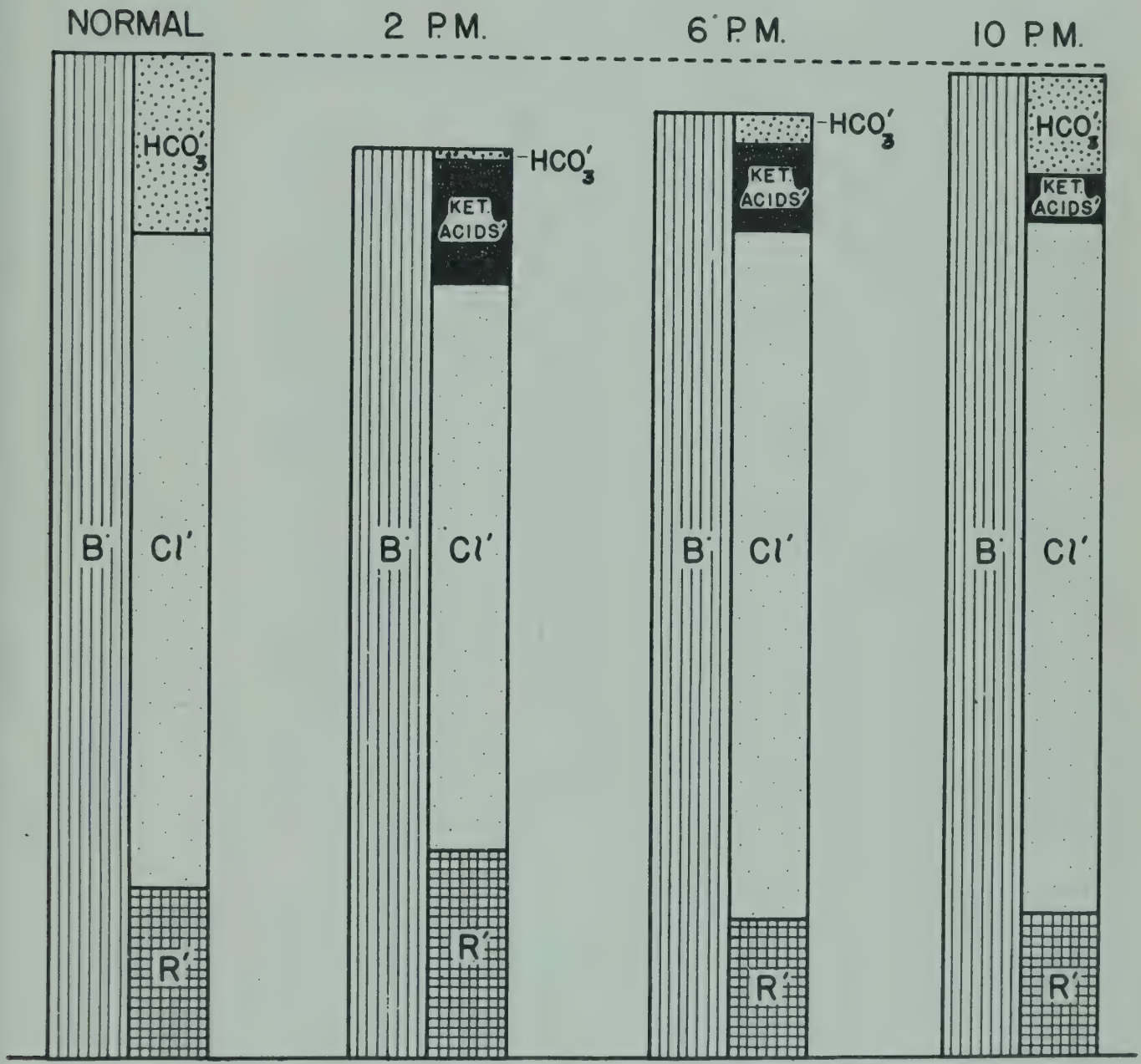
therapy of severe states of dehydration.

Direct support of extracellular bicarbonate should be provided by intravenous infusion of a 1.5% (isotonic) solution of sodium bicarbonate when extensive reduction has produced acidosis of dangerous degree. The purpose of this procedure is to sustain bicarbonate until the reparative effects of salt (or salt-lactate solution) and glucose solution have been gained. It should be regarded as an initial step in therapy which will probably not need to be repeated.

The extent to which replacement solutions should be provided must be estimated for the individual patient with adjustment to a declining requirement as the objectives of treatment are approached.

The means at hand for replacement of the internal medium are, owing to the alertness and the capacity of renal regulation, extremely simple and practicable and are often quite dramatically life saving. The diagrams in this chart will serve to illustrate the rapidity of their effectiveness. The patient was a three-year-old child in diabetic coma, extremely dehydrated and with only a small remnant of plasma bicarbonate. As shown by the diagrams, an almost complete repair of plasma structure was obtained in the course of eight hours. Unseen in the chart, there was an equally important large progress toward restoration of extracellular fluid volume.

DIABETIC ACIDOSIS AND EFFECTS OF TREATMENT



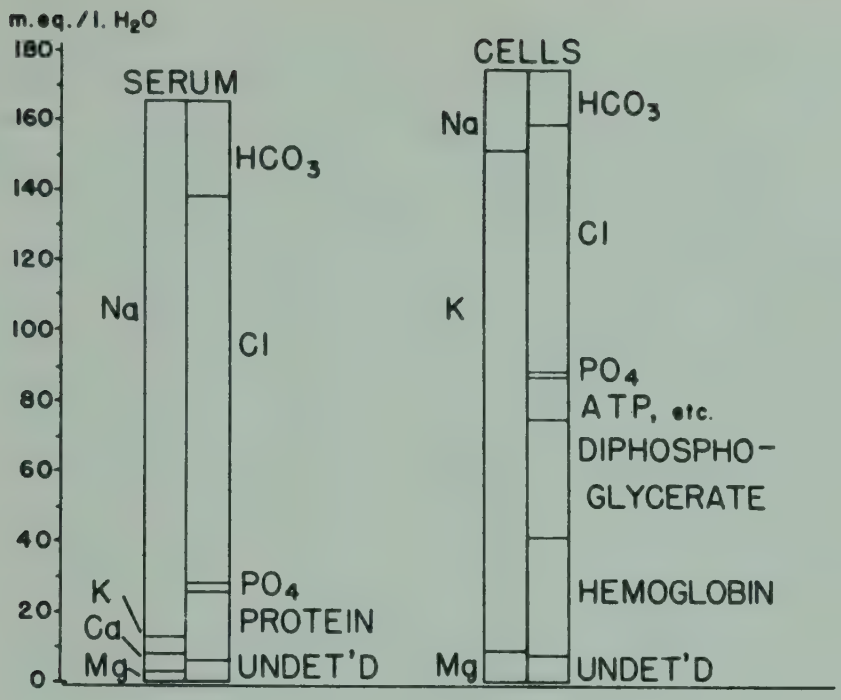
THERAPEUTIC AGENTS USED: INSULIN 25 UNITS, 5% GLUCOSE SOLUTION (INTRA V.) 300 CC., 2% SODIUM BICARBONATE SOLUTION (INTRA V.) 200 CC., 0.9% SODIUM CHLORIDE SOLUTION (SUBCU) 300 CC.

CHART 51

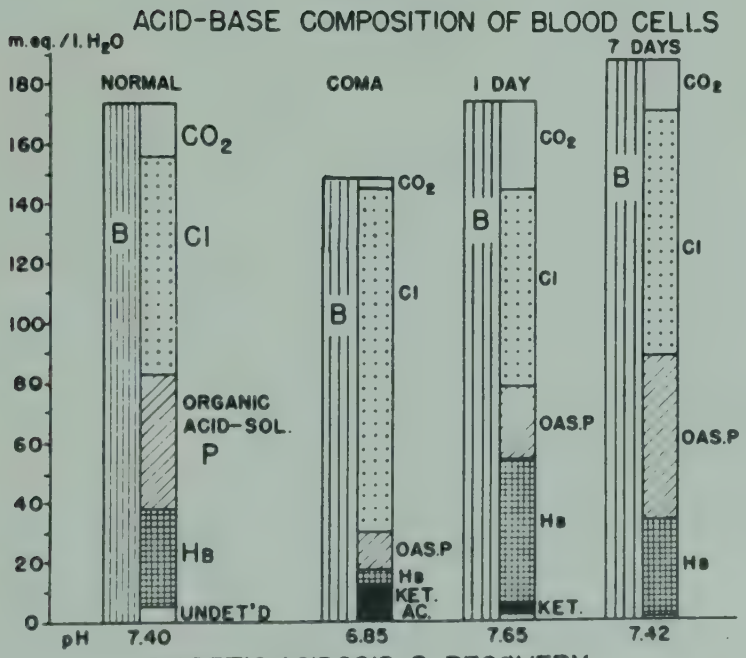
The charts in this syllabus give, in some measure, an account of the regulatory mechanisms which defend, and of the pathological processes which disturb, the physico-chemical constancy of extracellular fluid. This constancy is the basis of integrity of chemical structure and of chemical transactions within the tissue cells. The diagrams in this chart, constructed by Guest and Rapoport from their dissections of the chemical anatomy of red blood cells, are added because they so excellently illustrate the dependence of normal intracellular structure on physico-chemical stability in the surrounding medium. In figure 1, the normal values for the cations and anions in serum (or plasma) and cells are given as milliequivalents per liter of water, taken as 93% for serum and 70% for the cells. The bulk of the base in the cells is potassium, but they also contain sodium and, in much larger measure, chloride, and so differ with respect to these two ions from tissue cells (chart 2). The organic phosphates (adenosinetriphosphate and other acid soluble organic phosphates together with diphosphoglycerate) and hemoglobin constitute, on the anion side, a much larger value for non-diffusible components than do the plasma proteins. Owing to the multivalency of these substances, their ionic concentrations are much smaller than the values for combining equivalence shown in the diagram. This discrepancy between concentration and equivalence for the organic ions being larger in the cells than in plasma, produces the osmotic requirement for adjustment of the concentrations of the inorganic ions, which will provide total ionic concentration equality with plasma and also preserve total cation-anion equivalence. As shown in the chart this adjustment produces a higher total base concentration in the cells. So that, although the cells have their own ionic pattern, the over all dimension, total ionic concentration, rests on the value sustained in extracellular fluid.

The changes in the chemical structure of blood cells from a patient in diabetic coma and during recovery are recorded in figure 2. A conspicuous change is a large reduction of base. This can be credited to the osmotic effect of fall of base concentration in the plasma (see preceding chart). In other words, reduction of (Na) in plasma compels removal of K from the cells, unless adjustment of concentration is gained by increase in cell volume. Actual withdrawal of intracellular base in diabetic acidosis is shown by the large increase of excretion of potassium in the urine observed by Atchley and Loeb. Striking changes are seen on the anion side of the diagram. There is large recession of base equivalence of the non-diffusible components, hemoglobin and the organic phosphates. Both of these changes are referable to the extensive shift of reac-

1.



2.



DIABETIC ACIDOSIS & RECOVERY

CHART 52 FROM GUEST AND RAPOPORT

tion in the direction of acidity. Increase of hydrogen ion concentration reduces the base equivalence of hemoglobin without altering its concentration; in the case of the organic phosphates, the enzyme-conducted reactions which build these substances are altered in the direction of degrading them to inorganic phosphate, which enters the plasma and, as Guest and Rapoport have shown, is removed in the urine. The resulting extensive reduction of base equivalence of non-diffusible components is covered by further entrance of the diffusible ions, chloride and bicarbonate ion, into the cells, in terms of the requirement for total ionic equilibrium with plasma. This will also involve some removal of base acccrding to the change in the relative concentrations of the non-diffusible ions in plasma and cells. Deficit of anion is replaced chiefly by chloride owing to its relatively large concentration in the plasma.

Failure of the regulatory mechanisms which govern extracellular fluid to sustain its normal osmotic value and hydrogen ion concentration thus brings to pass the extensive changes in the chemical structure of the red blood cells shown in these diagrams. Changes in tissue cells are not so accessible to study. These cells contain organic phosphates and other organic substances, the synthesis and interactions of which are governed by enzymes. A prime requirement of this enzyme control is stability of pH. Change in reaction will cause change in the quantity of these components and in the base equivalence of the cell proteins. Change in total ionic concentration in extracellular fluid will command corresponding adjustment of the intracellular value. Here it may be noted that, according to chart 2, intracellular ionic concentration does not have the support of the chloride transfer seen in the red blood cells. That extensive structural changes do occur is shown by the large excretion in urine of potassium and of inorganic phosphate found in diabetic acidosis and in other states of disturbance of the milieu interieur.

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The data used in Charts 45-49 are from unpublished studies on the life raft ration by Butler, A.M., Gamble, J.L., Talbot, N.B., MacLachlan, E.A., Appleton, J., Fahey, K., and Linton, M.A., Jr.